

djj

DJJ

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Devices and Radiological Health

NEUROLOGICAL DEVICES PANEL

Tenth Meeting

Friday, June 27, 1997

9:30 a.m.

Room 030
9200 Corporate Boulevard
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

P A R T I C I P A N T S

Committee Members:

Chairman:

Harold A. Wilkinson, Ph.D., M.D.

Voting Members:

Alexa Canady, M.D.
Everton Edmonson, M.D.
Gilbert Gonzales, M.D.
Andrew Ku, M.D.
Marc Nuwer, M.D., Ph.D.

Deputized Voting Members:

Michael Deveraux, M.D.
Steven Piantadosi, M.D., Ph.D.
Orlando Snead, III M.D., F.R.C.P.
Susan Spencer, M.D.

Industry Representative:

Sally Maher, Esq.

Consumer Representative:

Anne Wojner, M.S.N.

On Behalf of the Food and Drug Administration:

Levering Keely, Jr., R.N., Executive Secretary
Thomas J. Callahan, Ph.D.
Daniel A. Spyker, M.D.

C O N T E N T S

<u>ITEM</u>	<u>PAGE</u>	
Opening Comments, Levering Keely, R.N.		5
Call to Order, Harold Wilkinson, M.D., Ph.D.		6
Introduction of Panel Members, Harold Wilkinson, M.D., Ph.D.	6	
Conflict of Interest Statement, Levering Keely, R.N.		8
Old Business, Levering Keely, R.N.		11
Open Public Hearing:	12	
Statement of Tim Fabian	12	
Statement of Paulette C. Machara, CEO, Epilepsy Foundation of America	15	
Statements of Nancy and Albert Jean		20
Statement of Robert Cassidy		25
Statement of Patricia Kroboth		32
Open Committee Discussion: Pre-Market Notification: Implantable Stimulator for the Treatment of Seizures	39	
Firm Presentation: Cyberonics		39
William Duffell, Ph.D.	39	
Steven Reid, M.D.	46	
Marty Salinsky, M.D.	52	
Thomas Henry, M.D.	63	
Dean Naritoku, M.D.	68	
FDA Presentation	115	
Frank Lacy, MSE, FDA Reviewer		115
Ann Costello, Ph.D., D.M.D., FDA Reviewer		119

djj

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

djj

CONTENTS (Continued):

ITEM PAGE

Panel Discussion and Vote:	157	
Primary Panel Reviewers' Comments:		157
Michael Deveraux, M.D.	157	
Steven Piantadosi, M.D., Ph.D.		163
Orlando Snead, M.D., F.R.C.P.		166
Panel Discussion	171	
Final Vote	204	
Closing Comment, Levering Keely, R.N.		208

P R O C E E D I N G S

10:11 a.m.

MR. KEELY: It's now 10:11. We're starting late, obviously, because of the bomb threat. We'll try to push things along as quickly as we possibly can so that we can get out of here at the appointed time.

Welcome to the Tenth Meeting of the Neurological Devices Panel. I'm Levering Keely, and I'm Executive Secretary of the panel. First, a housekeeping item, which will be repeated later. Please, at the conclusion of the meeting, confine all trash to appropriate containers at the door of the room. For panel members, if you would leave any information from the firm that you have been reviewing at the desk, we will be glad to dispose of that at the end of the meeting.

If you have not already done so, please write your name legibly on the attendance sheet that's outside the back doors so that we can have an accurate record of those who have attended today. In addition, there is a packet of information containing an agenda and identification of panel members which is available outside for those who have not obtained this information already.

Let me call your attention to the format of the meeting today. The first session is open to the public, and

djj

we have an open public hearing concerning issues from the public from persons who have identified themselves to speak. Anybody who has made prior notification to speak is outlined in the Federal Register, which is dated May 21, will be given an opportunity to address the panel at that time. There have been several such requests.

Following this, if anyone else has a desire to speak, you will be recognized. Following the open public hearing, there will be an open committee discussion of the issues at hand. The involved firm will be given time for a presentation. The Food and Drug Administration will make a presentation, and the panel will discuss and vote on the issue at hand.

At this point, I would like to introduce Dr. Harold Wilkinson, the chairperson of the panel, who will preside.

DR. WILKINSON: Thank you.

I guess it's Mr. Keely. With all of the badges on your shirt there, I don't know whether to salute or say hello, but it's nice to have everyone here again, many of the panelists having been here before.

What I would like to do, especially briefly today, since we are starting late, is go around the table as we have done in the past; have each person give their name and

djj

affiliation and basically their reason for being here; for instance, I am a neurosurgeon, professor of neurosurgery at the University of Massachusetts in Worcester, Massachusetts. I'm Dr. Harold Wilkinson.

Dr. Ku?

DR. KU: My name is Andrew Ku. I am assistant professor of radiologic sciences at Allegheny University of Health Sciences Center in Pittsburgh, and my interest is in interventional neuroradiology.

DR. CANADY: I'm Alexa Canady. I'm professor of neurosurgery at Wayne State University in Detroit, and I am a neurosurgeon.

DR. SPENCER: I'm Susan Spencer. I'm a professor of neurology at Yale, and my specialty is the care of epilepsy patients.

DR. GONZALES: I'm Gilbert Gonzales. I'm a neurologist and neuroncologist at Mayo Clinic.

DR. CALLAHAN: I'm Tom Callahan. I'm director of cardiovascular, respiratory and neurology devices at FDA.

MS. MAHER: I'm Sally Maher. I'm director of regulatory affairs for Johnson & Johnson professionally, and I am here as the industry representative.

DR. SNEAD: I'm Carter Snead. I'm professor of pediatrics and neurology at the University of Toronto and

djj

have an interest in pediatric epilepsy.

MS. WOJNER: I'm Anne Wojner, and I'm president of the Health Outcomes Institute and an assistant professor at the University of Texas at Houston, and I'm your consumer rep.

DR. NUWER: Marc Nuwer; I'm professor of neurology at UCLA and department head of clinical neurophysiology at UCLA Medical Center.

DR. PIANTADOSI: My name is Steve Piantadosi. I'm a professor of oncology and biostatistics and a clinical trial methodologist at Johns Hopkins.

DR. DEVERAUX: I'm Michael Deveraux. I'm professor of neurology at CVRU in Cleveland and director of neurology at Mount Sinai.

DR. EDMONSON: Greetings. I'm Everton Edmonson. I'm a clinical assistant professor of neurology at Baylor College of Medicine and anesthesia at UT Health Science Center in Houston, and my area of interest is neuroncology, neurology and pain management.

DR. WILKINSON: Thank you.

Mr. Keely, you have a statement on conflict of interest?

MR. KEELY: I do.

I believe Dr. Piantadosi and Dr. Nuwer, you have a

djj

microphone between the two of you. It's not like one of these. It's a flat table mike.

We have a number of people who have been appointed to temporary voting status today. Pursuant to the authority granted under the Medical Device Advisory Committee Charter dated October 27, 1990, and amended on April 20, 1995, the following have been appointed by Dr. Burlington to serve as voting members on the Neurological Devices Panel for the duration of this meeting on June 27: Dr. Michael Deveraux, Dr. Steven Piantadosi and Dr. Susan S. Spencer. For the record, these people are special Government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at the meeting.

In addition, Dr. Michael Friedman, the deputy commissioner of the Food and Drug Administration, has allowed the appointment of the following individual as a temporary voting member also. Pursuant to the authority granted under the Medical Device Advisory Committee Charter of the Center for Devices and Radiological Health dated October 27 and as amended April 20, 1995, Dr. Orlando Snead has been appointed as a voting member of the Neurological Devices Panel for the duration of the meeting on June 27.

djj

For the record, Dr. Snead is a consultant to the Peripheral and Central Nervous System Drug Advice Committee of the Center for Device Evaluation and Research. He is a special Government employee and has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by committee participants. The conflict of interest statutes prohibit special Government employees from participating in matters that could affect their or their employer's financial interests.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interests involved, is in the best interests of the Government. We would like to note for the record that the agency took into consideration certain matters regarding Dr. Marc Nuwer. Dr. Nuwer reported that in the past, a colleague at his university was a principal investigator on the subject device. However, he has no personal

djj

involvement; no managerial responsibilities for his colleague or the department that was awarded the contract and has no personal relationship with the firm.

In the absence of any personal or imputed financial interest, the agency has determined that he may participate in the panel's deliberations. In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has financial interests, the participant should exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interests of fairness that all persons making any statements or presentations disclose any current or previous financial involvement with any firm whose products they wish to comment upon.

Thank you.

DR. WILKINSON: And then, you have old business.

MR. KEELY: Yes, we have two items of issue.

In September of last year, this panel reviewed a hand prosthesis, and we updated you at the last panel meeting. It was an implantable hand prosthesis. That prosthesis was recommended by this panel to be approved based upon several other considerations. It was given

djj

conditional approval. That has still not been approved as yet. The firm has just made a submission answering the questions of the conditions for approval. So, that is undergoing present FDA review at this time.

The meeting that we had in March concerned an implantable device being used for Parkinson's Disease and essential tremor. That also is undergoing review at this time.

I have no further issues to report on at this time.

DR. WILKINSON: All right; thank you.

Well, let's begin the actual panel meeting, and the first segment is the open public hearing. We have been informed of five names of people who would like to speak, and I have asked if Tim Fabian could be allowed to speak first because of travel constrictions.

So, Mr. Fabian, if you would like to address the panel.

MR. FABIAN: Good morning. My name is Tim Fabian. I live in Binghamton, New York. I appreciate the opportunity to be here to tell you about my experience with the NCP system.

I had surgery to implant this device in December 1995. The NCP system was activated in January of 1996.

djj

Since then, I have had no seizures. Prior to this device being put in, I had 10 to 15 seizures a day. Many seizures were focal seizures, affecting the left side of my body: twitching and shaking and stuff like that. I tried nearly all of the seizure medications. They didn't seem to work.

So, I went through a lengthy process in New York Hospital, and the doctors there found the area in my brain where the seizures were coming from. They told me to think about having them surgically removed. So, I thought about it, and I thought it might be a little dangerous, because if they get in there, and they touch something else, it might be more damaging.

So, the doctors agreed and suggested that I have this vagal nerve stimulator put in. Dr. Labar and I discussed trying this experimental device. As I mentioned, they implanted it. It worked very well for me. I feel great. I have no seizures now. I got my driver's license back. I feel able to get anywhere I want to without relying on any other people. I have more independence and feel like I am in more control of my life. I have gotten used to the side effect, which is--you heard it when I first started. Every 5 minutes, for 30 seconds, this goes off.

This device has helped me, and I hope you will consider approving this so that it can help other

djj

individuals with epilepsy.

Thank you.

DR. WILKINSON: Are you on medications now?

MR. FABIAN: Yes. I'm on three medications and plus this, and Dr. Labar on my last visit asked me if I would like to go off of one of my seizure medications.

DR. WILKINSON: Anyone else from the panel?

DR. CANADY: I was just wondering: since you have had the device in, have you ever gone off your medication?

MR. FABIAN: No; the medications I'm trying or on are some new medications that they found, Neurotin and Lomictol. The other one is Dilantin.

DR. DEVERAUX: Sir, other than your voice problem, have you had any other side effects?

MR. FABIAN: No, I haven't.

DR. DEVERAUX: None whatsoever?

MR. FABIAN: No.

DR. WILKINSON: All right; thank you.

MR. KEELY: One more question: could you disclose any financial involvement you have with the firm or any other firms?

MR. FABIAN: None.

MR. KEELY: Have they paid your way here?

MR. FABIAN: Have I?

djj

MR. KEELY: Has the firm paid your way?

MR. FABIAN: Yes--no, I mean, the Epilepsy Foundation paid for me to come here today.

DR. WILKINSON: Not the company.

MR. FABIAN: No.

DR. WILKINSON: Okay.

MR. KEELY: For any further speakers, if you could identify any relationships that you have with the firm, that would be appreciated.

MR. FABIAN: Thank you.

DR. WILKINSON: Thank you.

Then, representing the Epilepsy Foundation of America, Paulette Machara. I gather you're CEO of that foundation.

MS. MACHARA: Thank you very much.

Good morning, everyone. My name is Paulette Machara, and I'm the chief executive officer for the Epilepsy Foundation of America, and I very much appreciate the opportunity to appear here today on behalf of individuals with epilepsy who may benefit from the new implantable electrical stimulator, the NeuroCybernetic Prosthesis.

We hope that your review of the NCP system will find it safe and an effective device. We are excited about

djj

the possibilities that the NCP system represents, since it is the first device treatment option for epilepsy. The Epilepsy Foundation of America is the national organization that works for people affected by seizures and epilepsy through research, education, advocacy and service. Together with our 66 local affiliates, we monitor developments in the medical management of seizures and epilepsy very closely.

Approximately 2.5 million Americans of all ages have epilepsy. Of those, it is estimated that nearly one in three continue to have seizures that are not completely controlled with current available therapies. This leads to a diminished quality of life. In addition, for some, seizures are frequent and severe and can be life-threatening. In fact, status epilepticus, or a prolonged seizure, is potentially life-threatening, causing some 22,000 to 42,000 deaths per year, according to a recent community-based study.

Now, if you want to compare that to other popular causes today of diabetes, for instance, 48,000 deaths; female breast cancer, 43,000 deaths and AIDS at 29,000 deaths, this clearly is a very serious disease or disorder.

We receive some 30,000 calls a year to our toll-free service, often from families that are desperate for new solutions to their unresolved problems. The recent

djj

television movie First Do No Harm brought thousands of calls alone by adults and family members who were wanting more information about the ketogenic diet and its use in adults.

Uncontrolled epilepsy can cause considerable psychological, sociological and financial stress on individuals and families living with epilepsy. Living with the unpredictability of partially-controlled or uncontrolled seizures takes a toll on the individual and the family. Studies have shown increased dependence and lack of self-esteem can develop in children with epilepsy.

Continuing to have seizures results in a loss of driving privileges, which impacts mobility and can affect employment options for people with epilepsy. Unemployment and underemployment remain important concerns to youth and adults with seizure. Intractable epilepsy remains a very serious health problem.

As I mentioned earlier, current treatment options do not work for all individuals with epilepsy. Side effects of many of the current available medications can be quite disabling in some individuals and may adversely impact cognition and memory. Women of childbearing age have additional concerns. Many commonly-used antiepileptic drugs are human teratogens, yet most women with epilepsy must be treated throughout pregnancy in order to be protected

djj

against the adverse maternal and fetal effects of seizures. Maternal seizures may pose significant risk to mothers and the fetus. We cannot always predict which women will experience an increase in seizures during pregnancy.

The NCP system may be a unique opportunity for people with epilepsy. It does represent the first time a device has been developed to minimize or prevent seizure activity. If it can reduce seizure frequency and reduce the number of medications that an individual must use, people with epilepsy will benefit. It also offers patients self-management aspects, which are so critical to people with epilepsy.

The Epilepsy Foundation of America views it as a part of our mission to have individuals with epilepsy be advocates on legislative and regulatory policies that will affect their lives. Thus, we have asked individuals like Tim who have had an experience with this product to come forward and share their stories with you. We have paid for their travel and accommodations so that they can be here to talk to you personally this morning. But they are not serving as official spokespersons for the Epilepsy Foundation of America.

While the experiences that they describe today are generally positive, we recognize from the research that

djj

others have not experienced such dramatic reductions in their seizures. As you will hear, the NCP system is a positive development in the treatment of seizures. We believe that individuals with epilepsy are in the best position to speak of the impact of this product and their quality of life and how a reduction in seizure frequency can make a difference in employability, self confidence and overall wellbeing.

We recognize that this device is not a cure for epilepsy. It will not help everyone who implants the system, and we urge the company to continue their research on the device and other possible applications in individuals with epilepsy to more precisely identify who may be helped with this system. The Epilepsy Foundation of America does not endorse this product or any other treatment option for epilepsy. We rely on the FDA and the advisory committee to conduct a thorough review and make recommendations on the safety and efficacy of all treatments.

At the same time, we encourage rapid review of new drugs or devices, especially those designed to meet unmet needs. People with epilepsy will benefit from more frequent treatment options if they are adequately informed about the full extent of these options. We very much appreciate the opportunity to make comments about the NCP system, and I

djj

would just like to leave you with our disclosure statement:
The Epilepsy Foundation of America is a public charity. We solicit contributions from the general public, including corporations. We have periodically received donations from Cyberonics since 1993. We welcome these contributions to the cause of epilepsy and to the support of our work.

All EFA policy positions are developed independently and adhere to strict ethical principles and conflict of interest practices. As a matter of policy and practice, the Board of Directors of the Epilepsy Foundation of America who have a conflict of interest in a particular matter do not participate in that discussion or voting on that issue. And I would be happy to answer any questions that you might have.

Thank you.

DR. WILKINSON: Thank you, Ms. Machara.

Any questions from the panel?

[No response.]

DR. WILKINSON: This is certainly an organization that is doing a lot of good in this country.

MS. MACHARA: Thank you very much.

DR. WILKINSON: Nice to have you around.

MS. MACHARA: Thank you, Mr. Chairman. Thank you for your time.

djj

DR. WILKINSON: The next is, I understand it, a joint presentation: Nancy Jean and Albert Jean or speaking individually?

MS. JEAN: We would both like to make a small comment; nothing too long.

My name is Nancy Jean; this is my son, Albert. Albert is an uncontrolled epileptic. When Albert was 17 hours old, he started to have seizures due to a brain edema caused by a lack of oxygen at birth. The doctors were not sure that Albert would live. He was put on phenobarbital to control his seizures, and he remained on it until the age of 6 months, and although he was taken off the medication at that time, and he was a little bit slower than other children, he did develop normally.

At about 4 years of age, Albert would have episodes where he would get extreme headaches, be disoriented and confused. These were diagnosed as possible migraine headaches, because they only occurred every 4 to 5 months.

Six years ago, Albert was diagnosed as an epileptic because of several seizures he had in school. He has partial complex seizures as well as absence seizures, or auras, as we have come to call them. After being on every medication available and in several combinations, Albert has

djj

continued to regress in all aspects of his life. His health became an obsession with him, and his school work suffered considerably. Albert's self esteem was so low he told me several times he was going to kill himself or that he wished that he had never been born.

As a family, we all felt the effects of Albert's condition. Our four other children took on burdens that no other children should take on. They became Albert's guardians when we were not able to be with him. They have even had fights with other children who would make fun of Albert because of his condition. In essence, we all had epilepsy. Life became a constant struggle for us all.

For 2 years, Albert had several tests which showed no signs of seizures. The doctors told us that Albert was making up his seizures. Knowing Albert as we do, we could not accept this. We went to Childrens Hospital in Boston, where the doctors believed that Albert was an epileptic. He told us that surgery might be the only option for Albert, but he was ineligible for surgery because too much of his brain was involved in the seizures, and no focal point could be discovered.

Albert's neurologist gave us the chance to try the ketogenic diet. Unfortunately, it did not work, because Albert's system rejected it. We were not looking forward to

djj

the prospects of another medication. Albert had been on several with no long-term changes in seizure activity. He had also experienced several adverse side effects from the medications. We felt that Albert's chances of a normal life were running out.

When we were asked to enter the test study for the VNS, we were very cautious. After reading all of the literature for the stimulator, we felt that it might be Albert's only chance of ever achieving any kind of results. Albert had the implant surgery on March 6, 1996. The operation was a simple procedure. He went into the hospital on a Wednesday, and he was released on Thursday. He had very little discomfort but nothing major, and he was able to return to school the following Monday. The stimulator was actually turned on the second week of April.

We were told that it might take up to 6 months for us to see any results. Albert improved almost immediately. His seizures were less frequent and severe. We were amazed, and so was everyone else. Albert's teachers thought they had a new student. The month before the implant, Albert would take one step forward and two steps back. He improved so much that he made the honor roll for the last quarter of school.

He has started to become a typical teenager. He

djj

is more independent, self-assured and as cocky as all other teenagers. [Laughter.]

MS. JEAN: He has continued to make the honor roll for the entire eighth grade, and this year, he received the highest award at his school, which is the principal's award.

MR. JEAN: Do you have it

MS. JEAN: Yes, I do.

MR. JEAN: Do you want to show it

MS. JEAN: Not right this minute.

This is given for academic achievement and accomplishments that the student makes at the school.

Albert has been given back his life thanks to the stimulator, and it is our fondest wish that the stimulator be made available to all eligible patients, and we hope that being here today has helped in some small way.

Thank you.

Are you ready? Good.

MR. JEAN: My turn.

MS. JEAN: Your turn.

MR. JEAN: All right; before I had the stimulator implanted, I was very scared about my future. I could not ride my bike, go swimming or participate in a lot of activities and gym. I even had to have an aide walk with me in the halls at school, because if I had a seizure, I could

djj

get lost or confused. I was also embarrassed, because I was the only one in school who had a baby sitter.

My grades had dropped, and I became very frustrated. I hated taking so much medication. At one time, I was taking 24 pills of one medication plus two other medications every day. The medications did not help my seizures much, but they made me tired, clumsy and very angry.

Now, I could ride my bike, go swimming, walk to and from school alone and do a lot of other things I couldn't do before. My grades have gone from failing to honor roll. I do not have to take tons of medications either. I am so happy that the stimulator has helped me, and I hope that it can make other people happy, too.

Thank you.

DR. WILKINSON: Any questions from the panel?

Albert, do you notice any of the side effects on your speaking that we heard about from Tim?

MR. JEAN: Actually, when I was in the course for 3 years, and I got in--what is it?--a bravery award, and my stimulator comes on in practice, so, I had to swallow, and sometimes, I can't swallow, so, I am a little behind. So, I have to catch up.

MS. JEAN: Actually, he sounds better with it on

djj

than with it off as far as singing is concerned.

[Laughter.]

MS. JEAN: That's about all.

DR. WILKINSON: Any other questions from the
panel?

And financial arrangements, your way is paid by
the--

MS. JEAN: The EFA.

DR. WILKINSON: And not by the company

MS. JEAN: No.

DR. WILKINSON: Thank you very much

MS. JEAN: Thank you.

MR. JEAN: Thanks.

DR. WILKINSON: Robert Cassidy?

MR. CASSIDY: Good morning, ladies and gentlemen.

It is a pleasure to come before this fine board
this morning in order to attempt to place not only a human
face to the numerous facts and figures that will be
presented before you today but more importantly to give you
a human perspective on the vagus nerve stimulator and how it
has changed my life.

Personally, since its implantation on August 2,
1995, in order to provide you a clear, comparative point, so
that you are able to judge the effectiveness of this device

djj

and how it has been able to make a major change in the quality of my every day life, please allow me to give a very brief synopsis on the effect that having epilepsy has had not only on my life but, more importantly, how the effect has been altered by the implant of this device.

I developed epilepsy shortly after a car accident where I was struck by a drunk driver on July 4, 1973. I was only 17 years old and had just been granted a 4-year scholarship to Boston College on track. Due to the severity of the accident, my 4-year college scholarship was revoked. The medication that I was put onto at that time was phenobarbital but only in a small dosage. My neurological injuries were as extensively diagnosed as possible at that time, but the only medical equipment that was available in 1973 was an EEG readout, through which they were able to make as much of a recommendation as possible from.

As the years went by, the seizure activities increased along with the medications. By the time of the late 1970s or early eighties, my medications had increased to the point that I was taking three at the same time, 2,000 milligrams a day of three medications of Dilantin, Tegretol, along with the phenobarbital. My seizure activity had increased to the point of two to three seizures a month, the result of which, though the seizure activity was somewhat

djj

controlled by the medication, I walked around at times like a human zombie. I had bloodshot eyes; my coloration of my eyes had changed from blue to hazel; my short-term memory was affected, which resulted in having the effect upon my collegiate scholastic activities but more importantly the grades I had achieved or grades that I did not achieve because of it.

As the decade of the eighties progressed, I felt social impact of discrimination straight into my face. A senior vice president of a lending institution that I was one of the head loan officers for had told me within any future employment activities, never state I am an epileptic. I will either have two functions happen: I will not be hired for some reason that they may find out or create, or, secondly, it will affect my furtherance of employment within the corporation itself, for his sister had epilepsy, and that was how he told me, for society at that time had no ADA mandate to function from.

Excuse me.

For society at that time was repulsed by the epileptic and by the seizures that could occur, especially the grand mal seizure. What they seemed to portray was a sense of sympathy for the epileptic but an avoidance to commit day-to-day contact.

djj

Though my future wife at that time was well aware of my disorder when we got married in 1984, by late 1988, the stress in the marriage and subsequent effects finally proved too much for her to handle and was only one of the major reasons that led to our divorce in 1990. With the passage of the ADA Act, though, in 1990, my economic situation had become better solidified, but the seizure disorder did not.

No longer was the medication felt by some medical professionals at that time too heavily prescribed by way of it having warranted effects than my body had created a tolerance level against the medication. In 1992, I began a series of operational procedures that would hopefully alleviate the seizure activity by cutting off what was thought of at that time as a damaged portion of my brain. After a 2-year period of time, through four diagnostic operational procedures that had taken place, it was found that I could not qualify for the operation that was offered that would provide at least a partial cure for my disability. The reason that I did not qualify was that it was found that the damaged portion of my brain was within multiple areas and not just localized, as previously thought by Dr. Schacter at Beth Israel.

In 1995, Dr. Schacter proposed to me an

djj

experimental procedure of the implant in that he felt it could provide some positive results. Knowing what I had presently and that I was looking at a continuation of the same results without the implant, I jumped at the opportunity. For anything had to be better than the life I had led for the last 22 years as the result of the accident in 1973.

Since the implant in 1995, my seizure activity, though not completely curtailed, is close to being nonexistent. I have had only five known seizures since the operation in 1995, compared to some fashion of seizure activity occurring at least 25 or so times a year. My medication level has dropped from three known antiseizure medications to taking only one, that being Lomictol, 100 milligrams a day. Dropping from 2,000 milligrams a day to 100, believe me, is tremendous.

This has allowed me more freedom in the job market and in personal activities where, in the past, I continually watched myself to the point where I felt totally insecure of an individual's feeling toward me and my disability. Currently, I am a homeowner now, able to live on my own without fear of something occurring to me and not being able to help myself control the seizure. Finally, ladies and gentlemen, the implant of this device has provided me a

djj

giant step toward mainstreaming the epileptic in today's society.

Let me stress that today's epileptic does not want a handout. All he or she wants is an equal playing field to continue his or her life, and this device helps greatly in offering that chance. Please: I highly recommend its approval today by the vote that you all are to take.

DR. WILKINSON: Any questions from the panel?

You're still employed in the banking industry.

MR. CASSIDY: Yes, I am.

DR. CANADY: I'm just curious: have you turned off your stimulator at all and seen any differences?

MR. CASSIDY: Yes; at times, I have to do a great deal of public speaking; one of my personal hobbies is politics, and there aren't quite that many silent politicians around, and there are times--for I have a magnet, which I keep accessible, and I was told--and I have tried it a few times, though it helps stimulate the stimulator itself so it can help curtail the seizure activity, if you keep it totally monitored on the implant itself, it will not generate an influx; so, your voice does not--the vocal cords do not close; yes, it does.

I also found that if you take hot liquids, it helps keep the vocal cords open a little bit more.

djj

Are there any further questions?

DR. KU: Are you one of the patients who has auras and knows when your seizures are coming along?

MR. CASSIDY: The seizure activity that I have had through the years runs the whole gamut, from the auras to complex partials through grand mals. As far as auras are concerned, I usually--I have them about 80 to 90 percent of the time, usually, at some time--the one I've had most recently, which was less than a month ago; my aura, though, had occurred 3 hours before the seizure took place. But usually, my aura does happen, I would say, within 10 minutes prior to the seizure.

DR. WILKINSON: Yes, Dr. Snead?

DR. SNEAD: Have you had occasions to change the settings on the stimulator since it was implanted?

MR. CASSIDY: Yes, it has. My settings have been changed. Originally, it was on a 1-month level. Then, it moved to 3-months, and currently, it's on every 6 months. The next change of my settings will take place in October of this year.

DR. SNEAD: Do you know what kinds of changes were made?

MR. CASSIDY: I am not allowed that information.

DR. SNEAD: Oh, I see.

djj

MR. CASSIDY: I wish I was.

[Laughter.]

DR. WILKINSON: Yes?

MS. WOJNER: How often had you been hospitalized over the years before placement of the stimulator compared to after placement?

MR. CASSIDY: You mean upon each seizure occurring, being brought to the hospital? I would say about three or four times a year.

MS. WOJNER: And now?

MR. CASSIDY: Recently, it has been two times for--just through the fact that I happened to be involved as a passenger in a car that was in an accident. That was all. But at that time, because I do carry notification that I am an epileptic, they do it more or less for protection against any possible effects.

DR. WILKINSON: And again, your way was paid by the--

MR. CASSIDY: My way was paid by the foundation.

DR. WILKINSON: And not by the company.

MR. CASSIDY: Not by the company whatsoever.

DR. WILKINSON: All right; thank you.

MR. CASSIDY: Thank you.

DR. WILKINSON: And the last person I have

djj

awareness of as requesting to speak, Patricia Kroboth.

MS. KROBOTH: Good morning. I know I am listed as a patient; actually, my son is a patient. He is not here today. He has other problems such as cerebral palsy and neurological impairment which make it a little difficult for him to travel, but I am here to tell his story.

Seizures have controlled our lives for 25 years. My son, George, had his first grand mal at 7 months of age. By the age of 2, he was having several types of seizures numbering hundreds a day. He was hospitalized numerous times; had the ACTH injection series and was on the ketogenic diet. Since none of these attempts were successful, we enrolled in a government program for experimental anticonvulsant drug testing at the Neurological Institute in New York City. It was another unsuccessful experience.

For seven years, it was a matter of trial and error, with many combinations of old drugs and new. At age 7, the combination of valproic acid, phenobarbital and three bromides elixir would give George enough relief from seizure activity to attend school, but this period of time would prove to be the calm before the storm, the storm of his adolescent brain, adversely affected by the chemical changes of puberty.

djj

As the seizures began to increase in numbers and severity, so were the drug doses increased. Now into his teenage years, George would spend most of his time asleep. All quality of life had disappeared.

This would lead us to the Hitchcock Clinic at Dartmouth University and the corpus colossotomy. This split brain surgery would involve 4 months in and out of the hospital; recovery time would be 1 year. However, the surgery would prove to have little effect on the number of seizures, but it did lessen the severity for a couple of years while we continued to search for what we hoped would be his light at the end of the tunnel.

We have taken some extreme measures and made decisions that didn't come easily in the fight against intractable seizures. There were more than a few times when we thought that we would lose the fight. Many illnesses become deadly to a body already weakened by the side effects of high levels of anticonvulsant medications.

As poorly controlled as the seizures were, however, the one factor that allowed him to function at all was the combination of the three bromides elixir and valproic acid, but the elixir would not be available much longer; it was being taken off the market. Without it, his situation would be critical. Time and options were fast

djj

running out.

It was exactly at this point in time I picked up the newspaper one day and was immediately drawn to a picture of a teenage boy who looked exactly like George. The boy had the vagus nerve implant. As the result of this story, we were put in touch with the epilepsy center at New York Hospital. In sharp contrast to difficult decisions of the past, we walked into the doctor's office hoping George would be accepted for the program. For the first time, there would be no powerful drugs with all of their side effects to be considered. There would be no invasive surgery, with all of the complications that become a parent's worst nightmare. It was a simple surgical procedure that was having some quite remarkable results. For once, we had nothing to lose and everything to gain.

When George entered the VNI program, he was having five types of seizures that numbered hundreds a month. He was taking five anticonvulsant drugs. When the implant was turned on in April of 1995, George was not a rapid responder. We had waited 23 years; we could wait a little longer.

Slowly, over the coming months, we started to see a decrease in the numbers of seizures; then, a decrease in the types of seizures. The only side effect he has

djj

experienced is a slight hoarseness when the device is on. He has now had the implant for 26 months. We still continue to see improvement. In the past two months, April and May, we have twice seen a period of 19 days with no seizure activity. The last time we could make that claim, George was 9 years old. Up to today, the seizures for the month of June total one.

Of the five types of seizures that affected George, three have stopped altogether. They were focal, tremor and drop seizures. In the past, it was always the drop seizure that resulted in broken bones. Of the two remaining seizure types, the grand mal has been reduced from 11 a month to three; the petit mal or absence has gone from between 50 to 100 and most times too numerous to count to about six a month. The five anticonvulsant drugs are now three. The bromides elixir that we knew to be his lifeline is a thing of the past.

It is certainly an understatement to say his quality of life has improved. Before the implant, we would have to tie him in a chair if we left the room. To live with frequent, uncontrolled seizures is to live in a state of constant anxiety. When will it happen? Where will he be? Will he get hurt? To reduce the odds of possible and likely injury, you don't leave the house unless absolutely

djj

necessary; you don't even go in the yard.

Now, we can at last feel more comfortable taking George on outings or going out for an evening ourselves, knowing that George will be fine in someone else's care. The implant doesn't need to stop all seizure activity to change someone's life. George is excited to get up every morning and go to a workshop. He is proud to bring home his paycheck. He loves the slot machines in Atlantic City. Last month, he went to his first baseball game with his coworkers. Tomorrow, he is going to the Hilton Hotel for an overnight respite weekend, and last but not least, he looked at me the other day and said he was happy.

Don't turn out the light at the end of the tunnel for so many who still search. Thank you.

DR. WILKINSON: Questions, comments from the panel?

[No response.]

DR. WILKINSON: It sounds as if your family has held together, despite this tremendous strain.

MS. KROBOTH: Well, I was divorced from George's biological father, and I am remarried, but my second husband has adopted George, and that was 10 years ago.

DR. WILKINSON: Certainly, the strain on the whole family is an important part of this disease.

djj

MS. KROBOTH: Absolutely; I think it was like Nancy Jean says. Everybody has epilepsy in the family.

DR. SPENCER: Was George placed on any new seizure medications over these past 2 years?

MS. KROBOTH: Yes; I think Neurotin was one; Lomictil. He was always on five anticonvulsant drugs. The fifth drug was always whatever new drug we were trying at the time. It's only, you know, in the past few months that we are down to three drugs. Like I said, George's best response from the implant really happened in the last 3 months, although the seizures, the activity, the seizure activity, the number and severity slowly decreased over 2 years, but it was really in the last 3 months that we've seen the most response.

DR. WILKINSON: Yes?

MS. WOJNER: I would imagine that caring for someone like George would produce a fairly substantial amount of financial stress on your family. I am curious to know: have you noticed that some of those financial concerns have been reduced since the implant because of less health care utilization?

MS. KROBOTH: I did not ever have any help with George. I don't work, and I just helped him live his life. So, technically, I was not ever involved in health care, but

djj

I provided it all myself. So, George not only has a better quality of life; I sort of have mine back, too.

DR. WILKINSON: And again, your way was paid by the Epilepsy Foundation.

MS. KROBOTH: By the Epilepsy Foundation.

DR. WILKINSON: And not by the company.

MS. KROBOTH: Correct.

DR. WILKINSON: The Epilepsy Foundation; all right.

Thank you very much.

MS. KROBOTH: You're welcome.

DR. WILKINSON: Now, those were the only names I was given as persons who asked in advance to speak. Is there anyone from the audience at present who would like to speak today?

[No response.]

DR. WILKINSON: All right; hearing no request, then, and in view of the late hour, I think we've already had our break for the morning.

[Laughter.]

DR. WILKINSON: And so, let's move on into the open committee discussion, and the first item there is the firm's presentation.

MR. KEELY: If throughout the presentation, both

djj

the firm and then the panel members could speak directly into the microphone, the transcribers would have an easier time trying to pick up the questions that are being asked.

[Pause.]

DR. DUFFELL: Good morning, Dr. Wilkinson and members of the panel. It is a tremendous opportunity for us to be here to present a presentation to you on behalf of Cyberonics, and I would like to thank you all for the tremendous effort you made, considering the weather last night, in getting in here and staying this morning, considering the risk that we might have about us.

[Laughter.]

DR. DUFFELL: I've been looking at this podium here wondering if the dogs sniffed underneath this thing.

[Laughter.]

DR. DUFFELL: But in any case, we are here today for an important reason, and I appreciate your presence.

I would also like, before really getting started into the presentation, to extend a special thanks to the members of the FDA staff for their rapid consideration of our PMA application and making a very good decision, we think, certainly, probably a biased perspective on that, in bringing us here today. In particular, we would like to thank Dr. Spyker, Dr. Costello and Mr. Lacy for their

djj

tremendous efforts, in our opinion, way above and beyond the call in the review in getting the decision made to bring us here today.

DR. WILKINSON: Was that your stimulator?

DR. DUFFELL: Yes, it was--no.

[Laughter.]

DR. DUFFELL: Also, before getting going, I would also like to turn to the patients who spoke this morning. It's really important that their point for me this morning really drove home for me what we're here today and what we're in business for and how important our decision is today and what happens to this product, and I do thank you all for your remarks.

Cyberonics would initially like to provide the panel with the basic overview of the NCP device and the system and our clinical data, and we would like to kind of ask that during this initial presentation that will last about 30 minutes if possible to hold your questions until the end or after the FDA has made their presentation.

I would start off by saying that just like in 1958, with the introduction of the pacemaker technology to treat the electrical malfunction of the heart, the NCP system is not too unlike that in that it is an electrical device to treat an electrical malfunction of the brain.

djj

The quote that will appear up here before you on this next slide really confirms what we just heard from the EFA as well as the four people who spoke about their lives with epilepsy: that is, there is a need for new therapeutic options which first and foremost improve seizure control for refractory patients. The focus of our animal studies and human clinicals have been on just that: reducing seizure frequency in refractory patients. The results of our study highlight what the NCP system is and what it is not, and that has, as well, been highlighted by some of the patients this morning.

Most importantly, it is important that you recognize the company is not here today stating that this device is a cure for epilepsy. It is not. Nor is it a replacement for drugs in the approximately 70 percent of epilepsy patients who are adequately controlled by them. And finally, it is not a replacement for resective surgery for those patients in whom that procedure is qualified.

But what the NCP system is is a new electrical physiological complement to drugs and surgery. It is, as a takeoff from the indication that you will be considering today, another viable treatment option to inform physicians and refractory patients to reduce the frequency of seizures in adults and adolescents over 12 years of age as an

djj

adjunctive therapy in patients with partial onset seizures with and without secondary generalization.

With me today and behind me scattered throughout the audience are a number of invited experts that I have asked to be here today to help support Cyberonics in their presentation to you. These experts cover areas such as cognition, quality of life, mortality, various clinical studies, PET scan work that has been done to try to elucidate a measure of action; as well, individuals who are very experienced in the preclinical field, looking at, again, mechanism of action; a neurosurgeon familiar both with the implantation procedure as well as the complete and partial removal of the device and individuals who are very familiar with the cardiovascular effects of the device as well as a statistician to support our data analysis.

Also, of course, we have a number of Cyberonics employees here, covering issues such as engineering quality, manufacturing and, of course, clinical research.

A little bit about the company before we get going. We are a small firm, located out of Houston, Texas. What I would like to highlight on this slide is mainly just the last couple of bullets, and that is that I would like to make sure that the panel recognizes that this device is not brand new here for the United States and nowhere else; it

djj

has been marketed over in 17 other, different countries over the last several years. Presently, we enjoy a good regulatory status in all of those countries; have never had a product withdrawal or recall for any reason related to safety or effectiveness.

And then, as of today, we have approximately 1,000 patients worldwide who have been implanted with the device, with a total combined experience basis of approximately somewhere over 2,000 patient years. Our facility in Houston, Texas, is where we produce the product. All of the manufacturing is done there. Again, on this slide, what I would like to highlight are really a couple of factors here about our facility and the inspectional facility. The facility has been inspected by the U.S. Food and Drug Administration back in March of 1996 as part of the PMA review process and passed that inspection with literally no observations or remarks whatsoever.

Additionally, we are inspected periodically by KEMA, a notified body that inspects us for compliance to the medical device directives and ISO for quality systems, the most recent of those inspections having just taken place this past week, which was a little inconvenient considering the preparation for our panel today, but nonetheless, despite that, that inspection went well, and we have no

djj

outstanding observations from it.

As we refer to the NCP as a system, it is important that we point out to you at the start of this presentation what that system is comprised of. Most of the literature that you have probably read in preparation for the panel today really focuses on two pieces: the generator, which is implanted on the left side of the chest just below the clavicle and then, the NCP lead with the coils at the end, which connect to the vagus nerve. Also, we have a tunneling tool, which is used to create a passageway from the incision in the neck at the vagus location down to the generator. It's also used for placing the lead once the subcutaneous pathway has been created, and we have use of a programming wand which is connected to an IBM-compatible type computer. We recommend a dedicated unit for that for use for our proprietary software. The software is used, of course, to program the device, interrogate it and change the programming.

And then, we have also heard mentioned by one of the patients earlier speaking the magnet, which is another key, integral part of the system and part of the prescribed use, and the magnet, as we heard, also, has three basic functions: first, to provide on-demand stimulation for those patients receiving benefit as far as aborting or

djj

deintensifying the effects of a seizure; second, to test the daily functionality of the device; to make sure it is operating the way that it should; and then, finally, in the event, such as we heard from one of the speakers that the voice alteration effect could be a problem, to turn off the device for any reason that they might feel that there is a reason to do so.

This just gives you an up close view of our proprietary and patented helical coil design for our electrical lead. The sutures that you see on the ends of the lead are used basically for the placement of the coils around the vagus nerve. What I would like to do at this time is I have with me today a couple of examples of the device and a display box, which Brent is going to help me in passing around to you. I thought it was important, sometimes, to be able to actually pick up, touch and feel this thing that we're talking about today, and you will be able to see very closely the leads coiled in on the end. For any of you so inclined, there is even a little practice feature off on the side. You can take the tweezers and give your hands--especially the neurosurgeons--and see how quickly you can get that wrapped around that fake nerve to the left of the box.

The NCP system programming is fairly simple to

djj

operate for anyone who is familiar with computers and menu-driven programs. Basically, one cursor down through a series of selections; selects those and then, just before final programming is done with the device, a readout is given on the screen of the selections the doctor has made.

At this point, what I would like to do is break my presentation and hand over the podium to Dr. Steven Reid, who is a neurosurgeon, experienced both in the removal as well as placement of the device, and he will describe the surgical approach.

MR. KEELY: Each of the slides being presented by the firm as well as the FDA is in a packet that has been left for each of the panel members. So, if you need to refer to these slides, it's in that.

DR. REID: Thank you, Dr. Duffell, Chairman Wilkinson, distinguished members of the panel. I appreciate the opportunity to make this presentation to you today. I have no financial interest in the Cyberonics Corporation, but they did pay my way to come here to speak to you.

The procedure is performed for selected patients after routine presurgical evaluations. The NeuroCybernetic Prosthesis provides an additional tool for the neurosurgeon in his armamentarium against epilepsy. The entire patient system is implanted, with no transcutaneous leads, and so,

djj

patients can, therefore, participate in athletics and other activities unrestricted. The procedure has been done by neurosurgeons, vascular surgeons and other surgeons familiar with surgery within the carotid sheath. The NCP system implantation is fully reversible surgically.

Cyberonics provides training materials and an implant video to instruct surgeons familiar with surgery in the carotid sheath in the implantation technique. Preoperative antibiotics are generally administered IV. The patients are positioned supine, with their head slightly extended and turned toward the right. Standard surgical preps are performed as for a carotid endarterectomy on the left side, and the field is extended to include the infraclavicular region.

Two incisions are made. One is infraclavicular, approximately 3 inches below the clavicle and is positioned below the planned site for the subcutaneous pocket. The scar that develops postoperatively, then, helps to prevent downward migration of the generator. The cervical incision may be performed like that of a carotid endarterectomy, parallel to the anterior border of the sternomastoid muscle, or it can be placed transversely at the surgeon's discretion. The platysma is opened, and the tunneling tool is then directed from the cervical incision to the

djj

infraclavicular incision to allow for passing of the lead.

Great care is taken in passing the lead subcutaneously through the tunnel in that the helical electrodes are delicate. The carotid sheath is then identified with blunt dissection and opened sharply. The vagus nerve is easily located between and deep to the common carotid artery and the internal jugular vein. The artery and the vein are gently retracted apart with blunt retractors, with the nerve identified and elevated with elastic vessel loops. The tether spiral and electrode helices are then positioned on the nerve, usually under magnified vision with loops or an operating microscope.

The loop is then placed in the lead to provide strain relief within the cervical incision and anchored to the cervical fascia using silastic tiedowns. The leads are then connected to the generator. The device is interrogated and tested with the wand and computer. Once adequate function and lead impedance is confirmed, the excess lead is coiled behind the generator and the generator internalized. A single suture is then passed through a special hole on the generator to anchor it to the fascia. The surgeon can then use a variety of cosmetic closure techniques. I recommend a subcuticular closure after closing the subcutaneous layers. The surgical time usually takes between 45 and 90 minutes.

djj

The patient may be discharged on the same day as the surgery.

The immediate postsurgical complications and problems include pain, which is common for all surgical procedures and is easily treated with PO analgesics. I was told by the group that there is an overall 7 percent infection rate in their entire experience, which kind of surprised me. At our institution, at the University of Florida, we have experience with 30 implants and zero infections. Only 1 and a half percent of the total series, however, has required explantation of the device. The remainder responded to antibiotic treatment.

Hoarseness, persistent, not related to the stimulation, occurs in approximately 1 percent of the patients and should be followed with immediate laryngoscopy and removal of the lead if the vocal cord is noted to be paralyzed; otherwise, it usually recovers. Hypesthesias in the form of numbness around the incision are probably due to division of cervical cutaneous nerves, and these also usually recover, as after any incision in that area, and rarely, a left lower facial paresis may occur, presumably due to division or traction on the cervical branch of the facial nerve.

Thank you once again for the opportunity to

djj

present this material, and I look forward to handling any questions you may have about the cervical aspects after the conclusion of the Cyberonics presentation.

DR. DUFFELL: Thank you, Dr. Reid.

Next, before getting into the clinical overview for the studies E03 and E05, I wanted to provide the panel with a brief overview of what our clinical program to date has been like. So, briefly, the company has conducted five well-controlled studies plus, additionally, long-term followup on these patients as well as a study in mortality.

The first two studies that were done were pilot trials or feasibility trials with very small patient numbers. This gave way to the first randomized, double-blind, active control clinical trial, which started in June of 1990 and ran through July. After that study, we started an open label trial for purposes of trying the device in other broader indications within epilepsy and a younger patient population. This was followed by the second double-blind, randomized control trial study E05. As I mentioned before, studies E03 and E05 will be discussed in greater detail further in this presentation.

Before launching into that, though, it is important that the panel recognize that the two double-blind control trials that were conducted did have some

djj

differences. The study objectives were slightly different, as indicated up above. More importantly, the exclusion criteria were different between the two trials. Study E05 excluded prior resective surgery patients. It also focused only on partial onset seizures with alteration of consciousness or a motor component counted, and it included a very exhaustive safety battery testing in there to assure that the risk-to-benefit ratio for the device was, indeed, in place.

We specifically focused in on Holter effects; pulmonary function; serum gastrin; urinalysis; chemistries and hematology, a whole battery of those safety tests.

We also did a slightly more exhaustive quality of life testing and assessments as part of the trial versus what had been done in E03, and unlike E03, the E05 study focused only on U.S. centers, 20 of them.

The low treatment parameter in the studies were slightly different, and, as always, in all of our clinical trials, we made a high focus on conducting the studies in compliance with good clinical practices standard to the industry.

At this point, I would like to hand the podium over to one of our E05 investigators, Dr. Marty Salinsky, and he is going to walk us through--wherever he is; there he

djj

is--he is going to walk us through the E03 and E05 study results.

DR. SALINSKY: Better.

Mr. Chairman, members of the panel, my name is Martin Salinsky. I'm with the epilepsy program at the Oregon Health Sciences University in Portland, Oregon. I am also a consultant to Cyberonics, Incorporated, and Cyberonics has paid my way to this conference.

In the next few minutes, I will review for you the results of two randomized, double-blind controlled trials of vagus nerve stimulation for the treatment of medication-resistant, partial-onset seizures. These two trials, E03 and E05, had similar designs. After a 3-month baseline evaluation period, all of the patients were implanted with identical stimulation devices. They were then randomized to receive either high-level stimulation, which was the presumed effective dose, or low-level stimulation, which was presumed to be less effective or ineffective.

Patients were treated for 3 months while they remained on their baseline doses of antiepileptic drugs, and the primary efficacy endpoint of this study was a comparison of the percent change in seizure frequency between the high and the low stimulation groups. This parallel group active

djj

control design was adopted in order to keep both the investigators and the patients blinded.

Both of these trials studied teenagers and adults with medically refractory partial seizures. The main difference between the two trials' admission criteria was that the E05 trial required a minimum of six seizures per month with an alteration of consciousness, whereas, the E03 trial simply required six seizures per month. There was no requirement for alteration of consciousness.

Patients with a progressive neurological disorder or an unstable medical condition were excluded from these trials, as were patients with prior cervical vagotomy or patients who had recently been enrolled in trials of investigational antiepileptic drugs. Additional exclusion criteria were added for E05. Patients with cardiac, pulmonary or active peptic ulcer disease were excluded from E05. Now, they were also excluded from E03 under the medical condition criteria, but this was specified in E05. Patients with two or more episodes of status epilepticus in the past year were excluded. This was in order to avoid the problems with seizure counting associated with episodes of status epilepticus. And patients with previous epilepsy surgery were excluded, including patients who had prior use of either cerebellar or thalamic pacemakers.

These are the baseline characteristics of patients in study E05. Approximately half of these patients were randomized to receive high-level stimulation, and the remainder received low-level stimulation. These groups were well-matched for age, sex, duration of epilepsy, number of antiepileptic drugs in use and the various subtypes of partial seizures, according to the ILAE classification scheme. They had longstanding epilepsy; they averaged 23 years' longstanding epilepsy.

The mean number of seizures per day was significantly higher for the group randomized to high-level stimulation, but the seizure frequency distributions were highly skewed; the distributions were non-normal, and the median rather than the mean provides a better measure of a typical patient's seizure frequency. The median was about one seizure every other day, and the difference between the high and low group was not statistically significant.

Here is similar data for the E03 study. This was a smaller study. It had a total of 114 patients. There were no significant differences between the high and low stimulation groups. In study E03, 115 patients were implanted, but one withdrew prior to randomization due to an informed consent problem. There were 114 patients in the efficacy population. 112 patients actually completed the

djj

study. One patient withdrew at about 6 weeks of stimulation due to a device malfunction, and another patient withdrew after 8 weeks of stimulation after suffering a non-fatal myocardial infarction.

199 patients were implanted under protocol E05. One patient withdrew due to a perioperative infection related to the device and was never randomized, leaving 198 patients who were randomized and activated. Of these 198 patients, one produced unevaluable seizure records, and a second withdrew consent prior to the actual treatment phase, so, there were 196 patients in the efficacy analysis. One additional patient discontinued stimulation after 8 weeks due to a safety concern. This was the occurrence of episodes of Cheyne-Stokes respirations in the postictal state.

Seizures were recorded in standardized seizure diaries, and the patients and caregivers were instructed how to classify each of the different seizure types according to the ILAE classification scheme. These diaries were collected at monthly visits and summarized by the study personnel.

Also, at each visit, adverse events were recorded, and this slide contrasts the high and low stimulation groups for both the E05 and the E03 study. I apologize for this

djj

very busy slide which is, I know, a bit difficult to read.

Hoarseness and voice change, as you heard earlier in the patients who gave testimony, were the most common side effects. These side effects only occurred during delivery of the actual stimulus train. They are current-related, and usually, they are not uncomfortable. Many patients also experience transient coughing, throat pain or shortness of breath during stimulus delivery, and again, this was limited to stimulus delivery; again, this was a current-related side effect, and it tended to decrease over time.

You will note on this slide that the adverse event reporting was higher in E05 than in E03. The reason was that E05 used a symptom reporting checklist, whereas, the E03 had adverse events reported only by interview. There were no significant central nervous system side effects during either of these studies, and there were no significant effects on serum gastrin levels, pulmonary function tests or Holter monitor results.

The effects of stimulation on throat muscles have occasionally led to swallowing difficulties: coughing or choking, usually with liquids; typically, at the very beginning of stimulation. Patients with preexisting swallowing problems could be at an increased risk for

djj

aspiration, and an appropriate warning has been recommended for the labelling.

There were no deaths during the E03 or E05 acute studies. However, there have been 17 deaths among approximately 1,000 NCP recipients worldwide, and this slide lists the causes of these deaths. Depending on your classification, somewhere between 3 and 10 of these deaths would be labelled sudden unexplained death in epilepsy or SUDEP.

And this slide gives you a comparison with recent studies in similar populations, and I will particularly draw your attention to the Lomotrogene and Gabapentin trials from 1995 and 1996. And it shows that the NCP SUDEP rate is similar to that seen in other groups of patients with refractory seizures. The rate as of August 1996 was 4.5 per 1,000 patient-years. An updated rate as of June 1997 is now 3.0 per 1,000 person-years.

Okay; finally, does vagus nerve stimulation work? Does it reduce seizure frequency in patients with medically-refractory partial seizures? And here is a summary of the results from the E05 study. I'll start up here on the upper right. The primary efficacy endpoint of this study was a comparison of the average change in seizure frequency between the high and low stimulation groups. And

djj

the decrease was 28 percent for the high stimulation group; 15 percent for the low stimulation group; and the difference between the two groups was statistically significant, confirming the study hypothesis.

This lower graph, which is very, very difficult to see, is a month-by-month breakdown during the course of the study. The implant is done at the arrow here, and the device was actually turned on a couple of weeks later, somewhere around here. What the graph shows was that by week 8, the high-stimulation group, which are the lower bars down here, have a consistent decrease in seizure frequency, whereas, the low-stimulation group, with the black circles here, has a smaller decrease in seizure frequency.

And finally, up here in the upper left hand corner is a within-group analysis. High-level stimulation produced a statistically significant decrease in overall seizure frequency; low stimulation did not.

Here is the same data for the E03 study; again, looking at the primary endpoint, there was an average 24 percent decrease in seizure frequency in the high stimulation group; a 6 percent decrease in the low stimulation group, and the difference between the two groups was statistically significant, confirming the study hypothesis. The month-by-month graph shows that high

djj

stimulation had a consistently more effective--was consistently more effective than low stimulation, and the within-group analysis shows a significant reduction in seizure frequency with high stimulation but not with low stimulation.

If we were to adjust the E03 admission criteria to mimic the admission criteria for the E05 study, we would lose 15 patients who had had previous resective epilepsy surgery. But the results are more or less the same: a statistically significant decrease in the high stimulation group relative to the low stimulation group, and the results are now nearly identical to the results from the E05 study.

Both of these studies used a visual analog scale global measure, where the physician, the patient and the companion placed an X somewhere along a 100-millimeter-long line that was anchored by the terms considerably worse, no change and considerably improved. And in E05, all of these ratings improved for both patients who received high stimulation and those who received low stimulation. But for the physicians and the patients, there was a significant improvement in the high stimulation group relative to the low stimulation group.

And a very similar pattern for the E03 study; in this case, the only significant difference between the high

djj

and low stimulation groups were for the physician global analog scale rating.

Additional quality of life measures were taken from the Washington Psychosocial Inventory; Health-Related Hardiness Scale; Quality of Life in Epilepsy scales and other scales. I am not going to review these in detail, but in general, the patients in the high stimulation group improved relative to baseline. Actually, 10 of their measures were significantly improved in the high group, whereas, only one measure was significantly improved in the low group. However, only three of 34 measured variables were significantly improved when the high group was compared to the low group.

And somewhat less extensive quality of life testing in the E03 study, but the overall pattern of results is similar. Seven of 23 variables were significantly improved in the high group, and two of 23 variables were significant improved in the low group.

Patients exiting the controlled trials were given the opportunity to continue vagus nerve stimulation in open-label extension trials, and over 95 percent of patients elected to continue treatment. During the open extension, the patients and the investigators were unblinded; all of the patients were turned up to the high stimulation

djj

settings, and medication changes were now allowed. This graph shows data from the E05 study and its extension, which was dubbed the XE5 study, and plotted over here on the left is the randomized control trial, with a 28 percent decrease in seizure frequency in the high stimulation group and a 15 percent decrease in seizure frequency in the low stimulation group.

At the time this slide was made, 88 patients had completed 6 months of therapy, and 40 patients had completed 9 months of therapy. And, in general, the trend is toward continued improvement in both groups: the high group, which had already started on high stimulation and the low group, which was converted to high stimulation during followup. However, this data is uncontrolled, and there are obviously several potential confounding variables, including medication changes.

Somewhat longer followup is available for the E03 cohort, but the pattern here is more or less the same. There is a trend toward continued improvement in both groups once they start on high stimulation. But again, this data is uncontrolled.

So, in conclusion, the results of these two randomized controlled trials were very similar. In each case, high-level stimulation was more effective than

djj

low-level stimulation in reducing the frequency of medication resistant partial seizures. Vagal stimulation was generally well-tolerated and in particular, it was not associated with the central nervous system side effects commonly seen with high-dose antiepileptic drug therapy and particularly with antiepileptic drug polytherapy.

And for these reasons, vagus nerve stimulation represents a much-needed option for patients who have failed antiepileptic drugs and perhaps those who are not optimal candidates for epilepsy surgery. These clinical trials support the requested indication for use in reducing the frequency of seizures in adults and adolescents over 12 years of age as an adjunctive therapy in patients with partial onset seizures with and without secondary generalization.

Thank you for your attention.

DR. DUFFELL: Thank you, Dr. Salinsky.

That basically concludes the formal portion of our presentation. At this time, I would just like to ask the panel to keep in mind that I have one speaker, Dr. Thomas Henry, who appeared on one of the first slides who has done some extensive work in PET-scan analysis as it relates to possible mechanism of action. He will have to leave in approximately 20 minutes, so, I'll leave it to your

djj

discretion as to whether or not anyone has an interest in that. They may want to ask him his questions sooner rather than later.

Otherwise, thank you for your attention, and we stand ready to answer questions later today.

DR. WILKINSON: Does he have a formal presentation that is brief?

DR. DUFFELL: It wasn't a planned portion of our formal presentation. It was a planned response to questions regarding the mechanism of action: how does the device function; what does it do.

DR. WILKINSON: It sounds as if since you've raised that question, that's a given, particularly since we have not heard any animal data, and we have heard no basic physiological background, it might be good to hear something about that aspect of science.

DR. DUFFELL: Okay; fine.

Dr. Henry?

Dr. Henry is from Emory University in Atlanta, Georgia.

[Pause.]

DR. HENRY: Thank you, Mr. Chairman and panel members. I should mention that my way was paid by Cyberonics for this meeting. Additionally, I was the

djj

principal investigator for the E05 site at Emory University, which was funded by Cyberonics. I also designed, together with the PET physicists or positron emission tomography physicists at Emory a study of selected E05 patients at Emory, and that study was additionally funded by Cyberonics.

This study was proposed in order to look at potential sites of blood flow change that would be induced by acute vagus nerve stimulation with scanning using oxygen-15 water PET techniques. In each case, each subject had an injection of 60 millicuries of oxygen-15 water either performed with the vagus nerve stimulator turned off or performed with gating of vagus nerve stimulation by the magnet to induce stimulation beginning 10 seconds after injection of oxygen-15 water.

Image acquisition was performed for 60 seconds after the injection and would reflect about 60 seconds of cerebral blood flow averaged into each image set. Within each subject, one pair of scans was subtracted, such that a control scan was subtracted from a vagus nerve stimulation scan. Thus, there were three pairs within subjects. In the ultimate analysis, all of the scans were co-registered with each other within the telerac (phonetic) system of stereotaxic coordinates; thus, with five subjects in each group, we would have 15 pairs of scans. There were five

djj

subjects who received high stimulation parameters and five subjects in the low stimulation parameter group, using the standard stimulation parameters for the E05 study.

This was subjected, then, to T-statistical mapping. There was correction for repeated measures of testing within each data set, and I am only going to present results that were significant at a probability level of less than 0.05 after correction for repeated measures.

The results were similar in both groups. The areas of significance were identical, although the exact sites of some of the areas of stimulation were slightly different. All of these fell within the same structures. There was increased blood flow in the rostral portion of the medulla on the left side, which is the site of the vagus nerve stimulation in all cases and more dorsal and central aspects of this small area of the medulla oblongata.

Additionally, there were significant blood flow increases in the right thalamus; the anterior portions of the right parietal cortex; and locations that would relate well to the expected site of primary sensory cortex. The hypothalamus is a small structure for which the two sides cannot be adequately resolved with PET, but there did appear to be bilateral increase in the hypothalamus. On the other hand, increases in the anterior insula bilaterally were

djj

clearly defined as being independent on both sides as well as increased blood flow in the inferior portions of the cerebellar hemispheres.

Decreased blood flow occurred during vagus nerve stimulation relative to the control state in both hippocampi, both amygdally and bilaterally in the posterior portions of singulate cortex.

Based on extensive work in PET models of cerebral blood flow, it is expected that any such rapid increases in blood flow within the brain reflect predominantly increases in synaptic activity at the sites of cerebral blood flow, there being little other explanation for any such rapid changes in blood flow. It appears based on the sites of change that we saw in these studies that probably, the medullary sites of increased blood flow reflect the sites in the nucleus of the tractus solitarius and other medullary nuclei where the left vagus nerve has its primary synapses.

Additionally, we saw increases in sites that probably relate to somatasense reprocessing for left cervical sensation. After all, all of the individuals feel the tingling in the left side of their neck, and not unexpectedly, we saw increases in the right thalamus as well as what we expect was right primary sensory cortex.

On the other hand, we saw increases bilaterally in

djj

one autonomic structure, the hypothalamus, as well as in the limbic structure of the anterior insula, which is involved as well as systems for sensation of taste, which is mediated by the nucleus of the tractus solitarius and then bilaterally in inferior portions of the cerebellar hemispheres. We also saw significant decreases that likely are explained by decreased synaptic activity in bilateral limbic system sites, including the hippocampus, amygdala, posterior singulate cortex that are areas often involved in the ictal onset of complex partial and secondary generalized seizures or in the generation of the ictal dysfunction in these sites.

Overall, we observed changes in blood flow that cannot be explained just on the basis of unilateral sensory processing after stimulation of the left cervical sensory and vagal structures. Possibly, these areas of change may in part reflect sites where the therapeutic actions of vagus nerve stimulation may be operative.

Thank you.

DR. WILKINSON: Thank you; yes, Dr. Canady?

DR. CANADY: I was just curious: are there any circumstances where anybody has done any stimulation just of, say, the sternocloidal mastoid in the left to see what kinds of changes might be associated with that, so that we

djj

could separate out the diffuse from the focal? You could probably do it with a medial stimulator, I would think.

DR. HENRY: I'm not aware of any studies performed with electrical stimulation of any cervical or anterior thoracic structures. There have been a number of studies looking at electrical stimulation of sensory nerves, such as the median nerves in the upper extremities and other nerves as well, and those studies with cerebral blood flow PET using very similar techniques to those we used at Emory would consistently show increased blood flow in structures expected to be involved in somatosensory processing, for example, with left median nerve stimulation, studies consistently showed right thalamic and right primary sensory strip area activations.

DR. DUFFELL: If I may, one of our investigators, Dr. Dean Naritoku--

DR. WILKINSON: A little closer to the microphone.

DR. DUFFELL: One of our investigators, Dr. Dean Naritoku, has done some work that addresses your question; if you would like for him to address it now, fine; or, we can wait until later.

DR. WILKINSON: Well, it won't be much later. So, better come up now.

DR. DUFFELL: I was concerned only about Dr.

djj

Henry's getting his covered. I didn't really want to disrupt the FDA's presentation process too greatly. So, at the panel's discretion.

DR. WILKINSON: Let's go--

DR. DUFFELL: Now?

DR. WILKINSON: Well, we can always get Dr. Henry back on the griddle, so, why don't we keep the process moving.

Yes?

I think the panel is very interested in shedding some light inside the black box. If we have some idea of why this thing works, it would be comforting.

DR. NARITOKU: Mr. Chairman and panel, thank you for inviting me to speak. My name is Dean Naritoku. I am an associate professor of neurology and pharmacology at the Southern Illinois University School of Medicine in Springfield, Illinois. I have been an investigator in both the E03 and E05 studies and have been a consultant for Cyberonics. Otherwise, I do not have a financial interest in the company, and my travel was also covered by Cyberonics.

May we put up some slides? I thought what I might do is, just for the sake of brevity, just review some of the experimental data. I would be happy to expand on any

djj

particular points.

MR. KEELY: Is this new data that has not been included in the PMA before?

DR. DUFFELL: No, no, it's not.

DR. NARITOKU: It should be in there, but these are summary tables.

Like many anticonvulsant therapies, they are initially tested in various animal models, and what I have on here is a summary of effects in different seizure models and compared them to standard anticonvulsants and their profiles. And you will see, for example, vagus nerve stimulation is effective against pentylene tetrazol; maximal electroshock; strychnine seizures; kindled seizures, and it's effective against opposing the rate of kindling. This might compare similar in profile to a drug like valproic acid, which has a broad spectrum of antiseizure activity.

This also should be in the packet, but it is a summary of connections of the nucleus of the solitary tract. But one of the interesting things about the vagus nerve is that although it is a brain stem structure and a brain stem system, it has widespread projections to different parts of the forebrain, including areas that are very pertinent to epileptogenesis, including limbic structures, including reticular formation and including other structures within

djj

the brain stem that appear to have regulatory functions on seizure threshold, including direct and indirect projections to the locus cerulius and neuroenergetic nuclei and to the sertotenergetic nuclei.

Some early studies going as far back as the sixties and even further back have shown that vagus nerve stimulation can directly modulate EEG activities, either synchronizing or desynchronizing activity depending on the level of currents and also the level of anesthesia in the animal. This actually led to the initial hypotheses that it may be able to desynchronize brain electrical seizure activity. Whether that occurs in humans is less certain, I think, and on awake humans, we do not see, at least grossly visual changes on EEG; however, there have been some unpublished reports about spectral analysis evaluations showing a favoring of fast or frequencies during vagus nerve stimulation.

To answer your question about other metabolic areas, we have investigated in animals using 2-dioxyglucose, which is complementary to oxygen flow or water flow; this actually reflects glucose uptake in-brain, and this is just a representative cut of an animal that had vagus nerve stimulation--I'm sorry, a control animal and an animal that had vagus nerve stimulation while awake and freely moving.

djj

And if you look very closely, you can see that there is a slight reduction. It is hard to see, because it is a quantitative change. This is a very modest, 20 to 30 percent change, but there is a reduction of glucose uptake in animals that have received stimulation for an hour.

In this case, we have chosen an hour because, at least in animal models, it is a very efficacious anticonvulsant dose, and this is sort of very similar to what Dr. Henry has shown, that under chronic conditions, there are some specific areas of reduced metabolism, suggesting that there is direct inhibition in these limbic structures.

One of the other interesting things is that we saw reduced uptake in the solitary nucleus and in the locus ceruleus that might be counterintuitive and maybe different than what we would expect in acute stimulation. But, as I am going to show you, at least one investigator, Dr. Gale over at Georgetown, has shown that the solitary nucleus itself can be regulatory on seizure threshold, so that inhibition of the nucleus is anticonvulsant, whereas, excitation with a drug like bicuculene is proconvulsant. So, certainly, down-regulation of this nucleus could be consistent with an anticonvulsant effect.

Now, we also have used foss labelling, and foss is

djj

a protein that is generated by neurons under conditions of higher activity, and this is actually a complementary mapping technique to 2-deoxyglucose. And the findings that we found were slightly different. They overlapped. Interestingly enough, we found an activation of noradronergic nuclei within the brain stem, the locus ceruleous and the a-5 nuclei.

To answer your question going back, has it ever been looked at stimulation of other parts, in this particular study, we went through every permutation we could think of. We implanted animals and did not stimulate them in case that the actual implantation process changed the function. We stimulated the nearby sternocloidal mastoid, exactly that, soft tissues and also stimulated the animals, gave them actual stimulation. And in this case, we did not see any specific labelling on either the sham stimulated or the nearby soft tissues, the sternocloidal mastoid simulation.

We feel that the connection to the monoaminergic nuclei as well as changes identified there during metabolic mapping suggest very strongly that this may be a potential mechanism for the anticonvulsant effect. We have also, one of my colleagues, Ron Browning, has looked at the effect of inactivating the monoamine nuclei, either by focal

djj

injections of a toxin, 6-hydroxydopamine, to the locus ceruleus or giving a toxin, a very specific serotonergic toxin, 5-7-dihydroxytryptamine, prior to stimulating the animals. And these drugs effectively reduced either the serotonin or norepinephrine and antagonized the effects of vagus nerve stimulation on induced seizures by pantalene tetrazol.

I would summarize the potential mechanisms including desynchronization of brain activity, inhibition directly of epileptogenic structures, perhaps in the limbic system, and modulation by monoaminergic systems and finally, potentially, inhibition of solitary nucleus for whatever secondary effects it has on seizure threshold.

Thank you. I will take questions.

DR. WILKINSON: Yes?

DR. SNEAD: Dean, have you ever looked at the effect of vagal nerve stimulation in any of the genetic models?

DR. NARITOKU: We only have preliminary data. What had initially tried was Dr. Woodbury's initial paradigm of 30 seconds before and 30 seconds after. We did not see a big difference in the genetically epilepsy-prone rats. Since then, we have found that there is a time-related cumulative effect of stimulation, so that if you stimulate

djj

longer and longer, the effect is much more profound. We have yet to go back and repeat that on the genetically epilepsy-prone rat. That is planned.

DR. SNEAD: And you saw antagonism with both noradronergic and serotonergic antagonists?

DR. NARITOKU: Dr. Browning has performed those. If you antagonize either one of those systems, that will oppose the effects of vagus nerve stimulation.

DR. WILKINSON: For the panel, I remind you that after lunch, there will be formal presentations from the FDA summarizing and analyzing the data. And then, later, our primary reviewers will give their impressions. But this is a good opportunity now to ask questions of the company. It won't be the only opportunity, but if panelists have specific questions about the presentation, this is a good time to do that.

So, shall we start on my right? Anyone--yes, Dr. Canady?

DR. CANADY: You mentioned in your presentation just now that in looking at the EEG results of humans that you didn't see any changes. Is there any electrophysiological data, either by telemetry or Holter monitoring of anything other than self-reported seizure frequency?

djj

DR. NARITOKU: I think the question arises whether they are by visual analysis or by spectral analysis, and I think the person probably best to answer it is Dr. Salinsky, who has actually done the studies on EEG. May I refer it to him?

DR. SALINSKY: We performed a study during the E03 protocol looking at spectral analysis of EEG segments before the stimulator was turned on, during stimulation and then after stimulation, so, this was not a chronic experiment; it was strictly an acute experiment in patients using the device. We looked at, I believe, six patients. We did not see any significant changes in background EEG. Now, this was not ictal EEG; this was background EEG.

There have been other reports, specifically from Dr. Uthman's group--I think he's here as well--and Dr. Hammond looking at EEG by visual inspection, and again, there do not appear to be any changes in the background EEG pattern. Nobody has yet investigated whether there are any specific changes in an ictal EEG pattern in humans. That would be, obviously, much more difficult to do.

DR. DUFFELL: Does that adequately address your question?

DR. CANADY: Yes.

DR. DUFFELL: Or would you like others to--okay.

djj

DR. WILKINSON: Other questions? Dr. Gonzales or anyone down the line?

DR. GONZALES: Question: I think it was Dr. Reid who mentioned that the infection rate was 7 percent for the implantation, and looking at some of the data that we just received here on page 437, but it is also listed in some of the handouts as well, that the adverse effects, adverse events for E05 high stimulation at 14.7; for E03 high of 3.5; and likewise, for the low stimulation in both studies, and the low E05, it was 15.5, and it was on E03 low, it was 3.5. And looking at all of the adverse events, the adverse events increased with the increase in stimulation, including infection, which I am a little surprised about, in that I'm just trying to think through why would higher stimulation produce such a large increase in infection rates? And that holds for both studies at both low and high.

Is it the stimulation, or is there something else that may be occurring, or do we just not understand?

DR. DUFFELL: I'd have to say on that one that I am not sure that it's something that we fully understand. The infection rate, I think, pretty much, as commented on by Dr. Reid, is probably somewhat site-dependent. As he mentioned, he has done 30 patients with no instances of that sort. You know, as far as the relationship to stimulation,

djj

I would really be at a loss to say why stimulation in and of itself would lead to that.

DR. GONZALES: It's a four or five-fold difference in infection rate.

DR. DUFFELL: Yes.

DR. GONZALES: So that if even higher stimulation rates are found to be effective, I mean, can we extrapolate that and say that we expect higher infection rate? We just don't understand; is that your point?

DR. DUFFELL: That would be my answer at present. Just a moment.

[Pause.]

DR. DUFFELL: Oh; the rates that you were referring to, the 14 percent off of that table, those are cumulative infection rates, by the way. Those are not necessarily surgery-related.

DR. GONZALES: Right.

DR. DUFFELL: In other words, if we had a systemic illness of some sort, it might be recorded as an infection. So, yes, those numbers could be misleading with regard to, I think, what your real question about is is there an infection related specifically to the device, rather than some sort of other intercurrent illness.

DR. GONZALES: Right; but even if you exclude the

djj

surgical procedure, which was exactly the same for both low and high, the increase in infection rate would then be related to stimulation. I mean, you would infer that--

DR. DUFFELL: Yes.

DR. GONZALES: --from what I'm seeing here.

DR. DUFFELL: Yes.

DR. WILKINSON: Also, in the adverse events, there is a rather striking difference in vomiting reported in E05 as opposed to E03, which is not something, I think, that an interview would overlook. So, I don't think that could be instrument-related, related to the test instrument. But the milliamperage was higher in the E05 study than in the E03 study.

DR. DUFFELL: The high treatment settings were similar. It was the low treatment settings that were different.

DR. WILKINSON: Do you have an explanation of why one group had more vomiting?

DR. DUFFELL: We actually do believe that the use of the symptom checklist, which I actually have a copy of here if you would like to see it, but basically, I mean, at least in my clinical trial experience, I generally don't prompt people by asking them have they had vomiting, nausea, headaches, so on and so forth. But in an effort to try to

djj

make sure that this particular study was a little bit more robust in assessing safety than the E03, we actually did do that, and we attribute--actually, there are several side effect profiles that have gone up on the E05 study, and we really attribute it mainly to the prompting that was done by the checklist very systematically going through and asking about all of these things more related to that. That's just a copy of what the symptom checklist looked like.

As part of the case report form, each investigator, during the interview actually concerted went through each of the areas and queried the patients on these.

DR. WILKINSON: Other questions from my right?

Dr. Ku? Dr. Spencer?

Across the table, any questions now?

Yes, Dr. Snead.

DR. SNEAD: I have a couple of questions of Dr. Henry, and then, I had a lot of questions of the company, but I don't know if I should wait until I give my comments this afternoon, because most of the questions are really related to the materials that we received rather than the presentation.

DR. WILKINSON: Well, since you are a primary reviewer, we will let you have that option of giving your review first and then asking the questions.

djj

DR. SNEAD: Okay; I'll do that this afternoon.

I just have a couple of quick questions for Dr. Henry. Is he still here?

Maybe I could put the questions to Dr. DeGiorgio.

DR. DUFFELL: Okay.

DR. SNEAD: And that is why is it that--maybe I'm incorrect; your group published a PET study similar to what he described, and yet, you got--it seems at least from the data that you published that you saw perhaps more localized changes than he described; is that correct?

DR. DEGIORGIO: Chris DeGiorgio, USC; no financial interest in the company; paid for by Cyberonics to come here.

Dr. Snead, actually, some of the results that Dr. Henry showed were remarkably similar. We did get ipsilateral cerebellar activation, and we got contralateral thalamic activation and contralateral neocortical activation. We did not see the changes in the frontal lobe or in the limbic system like he did, but actually, some of our changes were rather similar. But you are right: we only had four significant areas, but we used a P value. We defined significance at a P value of less than 0.0001 because of the multiple tests.

But overall, the core areas, contralateral

djj

thalamus and ipsolateral cerebellum were similar.

DR. SNEAD: I just have one other question, and then, I will reserve the rest of my comments for this afternoon, and that is that it is my understanding that there was an interim analysis in E03; is that correct?

DR. DUFFELL: Yes, there was.

DR. SNEAD: And what was the reason for that?

DR. DUFFELL: The company felt as though the results achieved at that particular time were sufficient to warrant premarket approval, so, they stopped the study earlier, submitted an application and then later completed the analysis once the full cohort had completed the trial.

DR. WILKINSON: Other questions?

DR. PIANTADOSI: Could I just ask a followup on that particular point? Is that to say that the company is watching the data and the results continuously as they accumulated?

DR. DUFFELL: No; not to my knowledge.

DR. PIANTADOSI: Was there a fixed prospective plan for monitoring the data in the study protocol?

DR. DUFFELL: Actually, there was, and I think our statistician might be able to address that issue. He was overseeing that process.

Jaye Thompson?

djj

DR. THOMPSON: Hello; I'm Jaye Thompson, and I'm a consultant for the company and have no financial interest other than that.

My understanding of the way that the interim analysis progressed--

DR. DUFFELL: Excuse me, Jaye? Dr. Henry was still here, so, the question really quickly, maybe? His cab is waiting, but he says he would love to take your question.

DR. SNEAD: Dr. DeGiorgio answered the question.

DR. DUFFELL: Okay; so it is taken care of?

All right; sorry.

DR. THOMPSON: Caught him at the cab.

My understanding of the way the interim analysis progressed is that the original protocol called for 25 patients per treatment group to be enrolled in the high and the low stimulation. I do not know exactly what prompted them. I would probably guess it was because it was the first time we had used this product in man. There became an interest to take a peek. For example, we had no idea what our response rates might be, what our variability might be. And so, a planned interim analysis was submitted to the FDA and the protocol amended to include that.

That analysis was then done when 37 patients had completed. The results; I believe the P value was around

djj

0.02, but the interim analysis required that the study would stop then only if the P value was a very, very small P value of 0.001.

They were doing corrections along the lines of the Fleming corrections, so that at the end of the study, when you enrolled all of the patients, you could still use the full alpha of 0.05. So, the study continued to enroll a total of what they hoped to be approximately 50 patients, 25 per group.

The next analysis was done when there were 67 patients. So, the study was actually completed at that time, at 67, and submitted. At the submission time, the FDA was concerned that we still hadn't treated enough patients, and they were more interested in making sure that we enrolled more patients. So, that study was informally just continued, and more patients were enrolled. And so, then, the next time the analysis was done was at the time of another submission, and, at that time, 113 patients had completed the study. So, any interim analysis was planned for and the P values appropriately adjusted for at the time of the interim. So, we feel that at the 113 or the 114 who are now available for analysis in E03 requires no adjusted P value and that 0.05 is approximately appropriate, and there was not that increased risk of type one error.

djj

DR. PIANTADOSI: Thank you.

DR. THOMPSON: Does that answer your question?

DR. PIANTADOSI: It does; thank you.

DR. WILKINSON: I had one question about the patient enrollment. Eighty-three patients were enrolled in these two studies and were not implanted. That is a significant percentage. It's somewhere close to 15 percent. Why were those patients enrolled and not implanted?

DR. DUFFELL: Many patients, you know, after having enrolled in it--we count--the strict criterion for enrollment is signing of the informed consent. That is how we counted it in both trials. And because of that, a lot of patients did take an informed consent upon being initially approached by a physician, signed the informed consent, and the moment they did that, I count that as an enrollment. Oftentimes, after reading the informed consent at home, considering it with their companions or whatever, many times, the patients decided they didn't want to undergo a surgical procedure for implantation of a device or for whatever reason, personal or otherwise, withdrew consent, basically, and didn't go on to participate in the trial.

DR. WILKINSON: Yes, Dr. Nuwer?

DR. NUWER: I have several questions, some, perhaps, more to the issue of which patients improved with

djj

this device. One would be was there an effective laterality of the epilepsy? For example, did left vagal nerve stimulation help to a greater degree with people with a right hemispheric epilepsy?

DR. DUFFELL: I'd like to maybe call on one of my clinicians to respond to that.

Dr. Salinsky, would you care to?

DR. SALINSKY: I didn't particularly look, actually, although that is a very interesting question, about the left/right difference. There were several post hoc analyses done to try to look for different subgroups. We may have a slide of that available. We may not have a slide of that available. There were well over 20 post hoc categorization analyses done. These were all post hoc analyses, so I don't think they're worth all that much. And none of these analyses showed particularly important effects; we certainly did not see an effect of epilepsy syndrome within the localization-related epilepsies, and I don't remember seeing a specific analysis of left versus right or left temporal lobe versus right temporal lobe. I think it is an interesting point, though.

DR. NUWER: Another question along these same general lines: did you look at the efficacy based upon which patients had epigastric auras or other auras that

djj

might have been related to autonomic function?

DR. DUFFELL: We did do analysis by seizure type, but I don't believe we have done the type of analysis that you're describing.

DR. NUWER: Okay.

Does this device also stimulate enough of the local structures in the neck that it stimulates the sympathetic nerves which are travelling with the carotid artery?

DR. DUFFELL: I'd like to maybe call on Dean Naritoku, if maybe he could comment on that from his clinical observations.

DR. NARITOKU: Well, I think it's hard to know whether they were stimulated or not. I think the best response to that is that there is extensive Holter testing and cardiac function testing on the E05 trial, and in that, there were no changes in rhythm seen; actually, no changes of heart rate, significant changes in heart rate were seen during the time of stimulation. So, I think that's the best index I can use, and that's probably the best estimate that I can give you, that there is no clinically symptomatic effects of that.

DR. WILKINSON: No mydriasis.

DR. NUWER: There's no change in the skin color or

djj

blushing; there's no change in--

DR. NARITOKU: I have to say I haven't looked for it specifically, but I have never seen it.

DR. NUWER: No pupillary changes.

DR. NARITOKU: I haven't seen any, no.

DR. NUWER: Has there been a study of the interictal activity in these patients? In other words, with a device like an ambulatory monitor to show that the rates of spiking or the rates of subclinical electrographic seizures are affected in any way by the use of this device?

DR. NARITOKU: I know in preclinical trials, it reduced the spikes both in pantalene tetrazol treated rats and monkeys with alumina gel foci. In terms of human clinical, I have to defer that.

DR. DUFFELL: No; I don't believe that we have any data of that particular type.

DR. NUWER: That's all I have.

DR. WILKINSON: Any other?

Dr. Piantadosi, one more?

DR. PIANTADOSI: Thank you; I have several. is that okay?

DR. WILKINSON: Oh, several; yes. We do need to break for lunch at some point, so, we can continue the questions after lunch.

djj

DR. PIANTADOSI: I won't ask them all, then, I am curious about some of the data that you haven't told us about, particularly study E04. Could you just tell us a little bit about efficacy and safety in that study?

DR. DUFFELL: Well, the material that I think you have in front of you does present the overall efficacy rates. I don't know if we've got a slide handy that summarizes that for us.

DR. PIANTADOSI: Well, maybe my question is more philosophical. Why have you chosen to highlight and present E03 and E05 rather than E04?

DR. DUFFELL: Okay; that I can appreciate, the E03 and the E05 being the double-blind, active-control trial was felt to be a little bit more robust as far as evaluating safety and effectiveness. We are perfectly prepared to discuss the E04 study, but it is an open-label trial with no control other than the patient's own match control from baseline, which was a short baseline.

DR. PIANTADOSI: Right; well, I felt pretty certain that that is what you would say. However, let me ask you the following: the randomization--let's just deal with randomization and then masking--the randomization in the other studies is between the high and low stimulation,

djj

which does motivate an unbiased, valid, high precision comparison of high versus low. But I might argue that that is really not a very interesting question. The real interesting question is efficacy, and as such, this study is not randomized with respect to efficacy, because it is a comparison of baseline versus post-treatment.

And if that is true, then, it seems to me that E04 is equally strong with respect to being able to draw inferences about efficacy. And if we pursue the same argument with regard to masking, it seems unlikely to me that anybody on the stimulator would be confused about whether the stimulator is on or off because of the side effects; therefore, the studies with respect to efficacy are also unmasked. Therefore, E04 should be contributing equally to inferences about efficacy. That is a comment.

DR. DUFFELL: Yes, and I can appreciate where you're coming from on that. I mean, we took great strides in trying to maintain what we thought was a very integrity-oriented blinding in the E03 and E05 studies. The purpose for the low treatment group was to give those patients a sensation of stimulation, so that in the event that they were--I mean, they knew something should be happening, that there was an electrical stimulus involved. We wanted them to have some sort of sensation that that

djj

phenomenon was actually taking place.

Of course, in the E05 group, that phenomenon took place much more frequently than it did in the low treatment group. So, I mean, we definitely feel as though the patients were blinded with respect to a high or low randomization during both of those studies, and further, we instructed the patients during their interviews with the doctors not to discuss the timing intervals for stimulation, and the device was temporarily cut off during those evaluations so that there would be no observed phenomenon, such the voice alteration that we heard earlier today by the physicians conducting the exams.

DR. PIANTADOSI: I don't disagree that with respect to high versus low, it is a randomized study, a randomized, masked study. I guess what I'm arguing is that that is really not a very interesting question for me as a panel member. I'm more interested in efficacy, and, in fact, some of the things you highlighted show the baseline versus post-treatment. That is the real efficacy. And with respect to that, the study is neither masked nor randomized.

DR. DUFFELL: Well, we did, of course, do the within-treatment--

DR. PIANTADOSI: Yes.

DR. DUFFELL: --analysis that you are talking

djj

about and the blinded trials as well.

DR. PIANTADOSI: Yes.

Let me ask you a couple of other methodologic questions as well. You showed fairly strong evidence, that being the differences between the medians and the means, both at baseline and post-treatment. Those are very different, indicating a high degree of skewness in the distribution of responses; in fact, somebody said--I forget who it was--during one of the presentations that the responses were highly skewed. Yet, the primary statistical outcome measures and tests of efficacy were based on T-tests, which are notoriously sensitive to skewness, and I wonder if you could tell us a little bit about why you did that rather than some transformed outcome or some other non-parametric measure of efficacy.

DR. DUFFELL: I'd like to call Dr. Thompson back to the podium, and I will let her address it from a statistical standpoint.

DR. THOMPSON: Again, I'm Jaye Thompson.

Seizure frequency, measured at baseline or during stimulation in all instances was highly skewed, not normally distributed, and that is expected; I have seen that in many seizure studies. But percentage change is very frequently normally distributed, and when you adjust for baseline, that

djj

mathematical adjustment makes it normally distributed, and that was very true in E03; the percentage reduction in seizure frequency is normally distributed; looks nice and normal and then in E05 as well. And so, our standard analysis approaches are valid. But in all cases, I think you will see--and our submissions and, I believe, in most of the panel packages, we would have non-parametric analyses side-by-side with parametric analyses, so that you can see that they were very complementary.

In E05, we did have some minor deviations due to potential outliers, but in each case, non-parametric approaches were used.

DR. PIANTADOSI: Since you brought that up, I was actually going to wait and ask about it later, but maybe this would be a good time to get my question answered. I can't dispute it, but I am a little surprised that the percent change, the way you calculated it, is normally distributed. I wouldn't have guessed that. And scanning down the list of patients that was provided to us in the supplemental packet, it looked to me like the tails of that distribution might be very fat.

Is that the case? Or is it, in fact, literally normally distributed?

DR. THOMPSON: It is very normally distributed.

djj

We used the Shapiro-Wilkes test and then, of course, also the good old eyeball test, but especially E03, there was no deviation whatsoever, and seizure frequency is normally distributed. And I have seen this phenomenon in other studies that I have worked in. Seizure frequency is routinely not normal when you just measure seizure frequency. That is highly skewed. But the percentage change, when, in essence, you are creating an outcome variable that is based on just the patients, then, you can imagine how it could be normally distributed, the response that you are seeing, because then, in other words, it is a response instead of a measure of seizure frequency, and it is normally distributed.

DR. PIANTADOSI: So, you didn't find any particular concern over some of the outliers on either end of the response distribution. I know there was one individual, I think, who had several hundred seizures and in one direction, a very positive change and in another direction a very negative change; no sensitivity to those kind of apparent outliers.

DR. THOMPSON: No serious deviations. Of course, we did do analyses where you included those and excluded them to see if the results changed drastically, and there was nothing of concern. There was one patient who was

djj

excluded from the analyses but not due to the fact that they were an outlier. It was due, rather, to the fact that they had inaccurate recording of seizure frequencies. That patient was included because of unreliable seizure counting.

But the other, we tried in all attempts to do analyses where we can include all of the patients. And then, just to make sure that we felt confident with our results, we did repeat the analyses, excluding those patients who could be considered as outliers to make sure that the results were reasonable, and they were.

DR. PIANTADOSI: You might be the right person to ask my last question about the death rate, the overall death rate on the studies. There seemed to be a little bit of inconsistency in the documents about exactly how many people died during the study period, and I think some of that was due to which set of studies you were talking about as the denominator. But my question doesn't relate exactly to the number but rather to the comparison group. You showed us a series of other studies in similar populations with roughly similar overall death rates. Are there adjustments in those series for the different ages of the patients in the studies?

DR. DUFFELL: The best person to answer that would probably be Dr. Annegers and Dr. Hauser, who did the

djj

independent evaluation of that.

DR. ANNEGERS: Fred Annegers, University of Texas Health Sciences Center at Houston. My trip was paid here, and I have received contract support from Cyberonics, but I have no financial interest.

As far as the death rates, we do have the table that gives the SUDEP rates for a number of studies. Those are all crude rates. They are simply cases over person-years. They don't take into account potential confounders, especially the severity of epilepsy, and should not be directly compared.

DR. PIANTADOSI: Do you have any idea at all if adjustments had been made for the age structures of the study populations or some attempts had been made to make those rates more comparable, how they would look?

DR. ANNEGERS: I can only surmise that it would lean towards the severity, given the severity and the duration of the complex partial seizures, the proportion of patients that either had surgery or were considered for surgery, and I think an adjustment would, in terms of comparing the Cyberonics cohort to the recent drugs, make the difference less.

I have been attempting to get agreement from the FDA and the various companies to allow a pooling of that

djj

data so that I could do an appropriate adjustment of age, etiology and other factors to answer that question more fully, but I can't right now.

DR. PIANTADOSI: Thank you.

DR. WILKINSON: Recognizing that we had no break this morning; that we had time for lots of extra coffee drinking before the session started--

[Laughter.]

DR. WILKINSON: --and that we do need to reconvene at 1:00 after lunch, if Dr. Deveraux would be willing to hold his questions until after lunch?

DR. DEVERAUX: I have one question.

DR. WILKINSON: One quick question; then, we can all have the bladder break.

DR. DEVERAUX: I would like to second Dr. Nuwer's question about laterality of the seizures and of the vagal stimulation, because it is interesting with the PET scanning data showing that there were some lateral changes.

My question is a more general one and maybe one to end the morning on and maybe even not appropriate for this type of a meeting, but I look at this device with concern about one area. Assuming that it is approved, it is actually rather simple to use. That is one of the things that you are talking about. My concern is that this is the

djj

type of device that should be used by the types of people who presented this morning: Dr. Salinsky, Dr. Reid and other people here who are in epilepsy centers who can deal with very complex seizure problems.

Has there been any thought, particularly from members of your study groups, into how this device should be handed out, literally? I worry about a neurologist someplace saying he's got a tough case to manage; he's sent to a neurosurgeon, and they slip in one of these devices outside the auspices of an epilepsy center and particularly neurologists and neurosurgeons dedicated to epileptology. Maybe Dr. Hauser or Dr. Salinsky or others in the room might want to comment on that.

DR. DUFFELL: I mean, I can comment briefly before Marty makes his statement that, I mean, certainly the intent of the company to make sure that the individuals who implant and treat with the device are adequately trained, and one of the things that we are striving and working with the agency over the labelling is to make sure that the labelling, of course, very appropriately says what the device is and is not capable of doing so that the expectations will be right.

We're not interested in seeing this thing prescribed like aspirin for the treatment of epilepsy. It would be counterproductive to our commercial success years

djj

from now to have that happen. So, with that, I will let Dr. Salinsky maybe additionally answer that.

DR. SALINSKY: I will just comment as a clinician, and I share your concerns. I don't think this situation is terribly different than the situation with the use of several potentially toxic antiepileptic drugs and, frankly, even with the situation involving epilepsy surgery, where one might be concerned that not every patient undergoing surgery is evaluated at one of the best centers prepared to do that surgery.

I think it will basically boil down to an educational effort through the company, through physicians who have worked with the device, through the Epilepsy Foundation of America, to educate neurologists around the country as to the appropriate indication and to make sure that surgeons who are implanting the device are well-trained with the implantation.

DR. WILKINSON: All right; we will, then, take our lunch break, and if we could, try to convene shortly after 1:00.

[Whereupon, at 12:28 p.m., the meeting recessed for lunch, to reconvene at 1:08 p.m.]

A F T E R N O O N S E S S I O N

DR. WILKINSON: If we could bring the meeting back to order, some of us want to make it home tonight and not have to adjourn to tomorrow. If we could bring the meeting to order, we had not closed the questioning session, so, I ask if the panel has other questions of the company before we begin the FDA presentations. I know I had one or two questions.

In the animal study data that was presented to us, there was a reference made to the risk of damage to the vagus nerve at the time of implantation if improper application was used, and I would like to know a little more about that.

DR. DUFFELL: Sure.

DR. WILKINSON: What is improper application, and how badly were how many nerves damaged?

DR. DUFFELL: I will call back on Dr. Reid, maybe, to explain what some of the complications could be.

DR. REID: I'm Dr. Steven Reid.

The question is what kind of complications can be seen with improper application.

DR. WILKINSON: That's correct.

DR. REID: The principal concerns would be damage to either the nerve or the electrode. Both are subject to

djj

damage if the technique is indelicate. The nerve itself could potentially be damaged through stretch, excessive retraction or excessive manipulation if any compression instruments are used on it. The lead can be damaged if it was improperly passed through the tunneler or improperly handled prior to its application around the nerve.

DR. WILKINSON: And how frequent is that likely to happen?

DR. REID: I think it is very unlikely to happen if the surgeon pays attention to the training materials and uses good surgical technique.

DR. WILKINSON: Another question that I had: I wasn't clear how the stimulation parameters were decided on. Why were these particular parameters selected for study?

DR. DUFFELL: Maybe I could call on Dean Naritoku, who has done some work about the on-off interval in animal models as to why the 30 seconds and 5 minute off interval was chosen.

DR. WILKINSON: And milliamperage, frequency, all of those other parameters.

DR. NARITOKU: Initial settings were selected on the basis of findings by Woodbury and Woodbury in animal testing, and what they have shown is that as they increase the frequency of stimulation from 10 to 20 hertz, they felt

djj

that the higher frequencies correlated more with anticonvulsant efficacy based on the shock and the pantalene tetrazol models. The initial on-off parameters were selected largely on the basis of two observations. One was, at least anecdotally or what was reported in the initial animals with status was that after they turned of vagus nerve stimulation, there would be a lag before the seizures came back. But it was really selected on the basis of what was thought to be a reasonable compromise between stimulation, safety and battery life.

Subsequently, some time curve studies that were done have shown that the effect of vagus nerve stimulation is persistent for several minutes, at least against pantalene tetrazol; a single stimulation of vagus nerve stimulation is about half maximal at 5 minutes after stimulation. So, at least in animal studies and followup, it seems like it's a reasonable interval to use. There are some investigators in Europe who have experimented with reducing the interval stimulation time, and they have reported, although not in a blinded study, that perhaps reducing the interval may be more efficacious. But that, we do not have complete data on.

DR. WILKINSON: The one other thing that I was uncertain about on the report of the clinical studies that

djj

we have, predictors of response included treatment baseline seizure frequency but also psychosocial or psychiatric disorders as being a positive factor. That could also be a negative factor if these patients were not accurate in their seizure recording. What does this have to do with epilepsy?

DR. DUFFELL: Well, with respect to the the seizure recording, remember that the requirement was that they be able to keep an accurate diary, either by themselves or by caregivers.

DR. WILKINSON: And who checked the accuracy?

DR. DUFFELL: The accuracy would have been checked by the investigator and study coordinators upon return to the clinics as to consistency in the way that they were recording the seizures. One of the great strides we are taking to make sure that everything remained the same so that we would have reliable and reproducible results during the course of the study, and that included at the start of the study, identifying on a one-on-one basis how a patient characterized certain seizures or the caregiver, if they were the one keeping the diary, how they characterized them. Then, the physician would, in turn, take that explanation of I get a warm, fuzzy feeling and then get dizzy and fall and characterize that into, of course, the International League definition, which we used for analysis purposes.

djj

But if you would like for us to further talk about some of the prognostic factors, I could call upon our biostatistician, who could perhaps give you some--

DR. WILKINSON: More of a philosophic question. Why is a psychosocial or psychiatric disorder a beneficial thing in the treatment of epilepsy?

DR. DUFFELL: I don't believe that at this point, I mean, we would view these kind of as ad hoc analyses that we have done in the database. I mean, certainly, the trial didn't set out to determine whether or not that was an important prognostic factor in determining treatment outcomes, and I am not sure, quite honestly, that we would have sufficient data within this cohort to say, indeed, that this is anything other than a spurious finding in the data and certainly, I would not think, should be anything relied upon for prescribing treatment.

DR. WILKINSON: Did you analyze without these patients to make sure they were not biasing your results?

DR. DUFFELL: Let me ask the statistician to respond to that, because I'm not sure of the answer.

DR. SPYKER: Dr. Wilkinson, while she is coming up--this is Dan Spyker--I should take the credit for that collection of factors in the labelling. I am eager to, in that section of the labelling which is relatively new,

djj

capture whatever we can to give an indication of which individual patients might respond. So, I think you are correctly criticizing each one of those factors, and, in fact, the lead reviewer is going to comment on that.

So, with your permission, I will take the credit for that silliness, and we can discuss it further after we hear his report.

DR. WILKINSON: All right; that would be a good way to approach it.

So, other questions from the panel before we proceed to the--yes, Doctor?

DR. KU: I noticed that the patients were free to turn their units on at will. Did that add significantly to the duration of stimulation?

DR. DUFFELL: You're talking about turning it on by use of the magnet.

DR. KU: Correct.

DR. DUFFELL: We did not do in the E05 study any concerted measurements about magnet effectiveness per se or how much that that may, indeed, have contributed to the overall observed efficacy rate. Really, what we would tell the panel is that it is part of the prescribed treatment regimen, if you will, and the observed effect, we presume, could only be reproduced in a clinic setting if you

djj

continued to use the magnet.

DR. KU: But that certainly affects the total amount of time that their brain is getting this type--their vagus is getting this type of stimulation. Was there any sort of study where you knew which patients were using, you know, doing the additional stimulation versus not? Because your stimulated population is a non-uniform population.

DR. DUFFELL: No, there was no specific data in E05 collected on magnet use itself.

DR. KU: Could have gotten that retrospectively from battery demand? I mean, many devices have a chip built in or, you know, at least preliminary devices to log the degree of use, or there is a demand switch.

DR. DUFFELL: Just a moment. Let me confer.

[Pause.]

DR. DUFFELL: My colleague was telling me that--I mean, the generator itself does capture information relative to the last 10 magnet uses, is it? Fifteen magnet uses. So, certainly, a physician--I tell you, why don't you come up and address that one? This is Brent Tarver from our clinical research.

MR. TARVER: Brent Tarver, Cyberonics.

The generator itself will show the date and time of the last 15 magnet activations. There is also a counter

djj

that increments every single time. So, if you come in at one visit, and it is 100 times, and another one, it's 150, then, you know they have used it 50 times between then. You can check with the patient, and if they say that they have used it 10 times, and it says 50 or 50 and 10, you can take the corrective action to go over with the patient how to properly use the magnet.

DR. WILKINSON: But you didn't use that as one of your analyses.

MR. TARVER: Not in the E05 study. Magnet activation was looked at in the E03 study. There is a subsection of patients who used the magnet that showed between the high and low group that they were able to abort seizures more successfully in the high group as compared to the low group. There was a subsection of the low group that, even though the magnet was turned off, they said that they could abort seizures using it.

DR. WILKINSON: Yes, Dr. Edmonson?

DR. EDMONSON: I've got three questions, one concerning battery life, the other cerebral dominance and the third, circadian concerns.

With regard to cerebral dominance, I guess you had mentioned that worldwide, about 1,000 of these stimulators had been implanted.

djj

DR. DUFFELL: Yes.

DR. EDMONSON: And I gather outside of the studies that are presented here that most of those were left-sided, left vagal.

DR. DUFFELL: They are always left.

DR. EDMONSON: Oh, okay.

DR. DUFFELL: Yes.

DR. EDMONSON: So, for right-dominant patients, left-handed, right-dominant patients, I was wondering if there is any analysis of those individuals to discern whether or not there might be some lateral dominant concerns with regard to certain adverse effects, speech or whatever.

DR. DUFFELL: Could you address that for me, Basim?

This is Dr. Uthman. Dr. Uthman actually happens to have the distinction of being the investigator here who has done the most treatment with the NCP device of all of the investigators present.

DR. UTHMAN: The answer is no, simply. But one thing that I would like to explain to the panel is that even with left-handed people, the left hemisphere is still dominant for speech and language in 60 to 65 percent of patients. So, even if we look at those patients, it is going to be close to a 50-50, and it won't show much

djj

difference.

DR. EDMONSON: Now, I think in one of the packets I observed a chart with the battery life according to the frequency and milliamps and so on and so forth. Over time, those who have extended after the study period and have had several adjustments of their stimulator, what is the average stimulation parameters and projected battery life?

DR. DUFFELL: The average milliamp output setting for most patients is around 1.25, and the amount of change that occurs over the life of the device is generally mild and limited, usually, to the output current.

DR. EDMONSON: So, if you were to make an average projection for battery life, the average refractory patient who gets this implant, what would the average battery life be?

DR. DUFFELL: We report on our current generator that we would expect about a 3 to 5 year battery life, dependent upon the programming settings. And, of course, to some very small effect, magnet use.

DR. EDMONSON: Okay; all right. And lastly, insofar as circadian factors, one of the studies looked at ultramonitoring and also acid production and that sort of thing from vagal stimulation. My concern would be during sleep, with some sympathetic activation removed that perhaps

djj

individuals may be more vulnerable to bradycardic episodes or sinus arrest and that sort of thing.

DR. DUFFELL: I would like to call on Dr. Bradley Vaughn from North Carolina.

DR. VAUGHN: Thank you for allowing me to participate in the panel discussion. My name is Bradley Vaughn. I am from the University of North Carolina. I was one of the E05 investigators; still currently am one of the investigators in the XE5. I have no financial interest in the company, but my travel was paid for by Cyberonics Corporation.

In regards to your question of the circadian rhythm and relationship to the heart rate, bradycardic events, what was found--and I'd be happy to show you a graph if you would like--is that there is a usual bradycardic increase in bradycardic events in the period between midnight and 8:00 a.m., and that is consistently seen both in the baseline time period and in the stimulation period or the test period. There were no increased risks or rates of bradycardia during that time period.

DR. EDMONSON: So, do you have a breakdown for both studies by stimulation level with--

DR. VAUGHN: I have the E05 data.

djj

DR. EDMONSON: Okay.

DR. VAUGHN: Let's see--thank you.

This is for the E05 study. I do not have the data for E03. I do not believe Holter monitoring was performed in the E03. But as you can see, the 8:00 a.m. to 4:00 p.m. slot, time period, relatively low events of bradycardia. 4:00 p.m. to midnight, obviously low; and then, as you get into both preimplant delta or the low stimulation and the high stimulation parameters, there are increased events of bradycardia. However, they are not statistically different between the groups, and that would be more likely related to the circadian rhythm of bradycardic events than the implant.

DR. EDMONSON: And so, the mean heart rate for the patients in the study versus our norm or the average patient, no seizures, normal--

DR. VAUGHN: No seizures, no medication, that analysis has not been performed in this study, obviously, because we used all patients who had epilepsy on one to three anticonvulsants. If I may, about my experience in research with regard to this, in general, patients who have epilepsy and are on anticonvulsants generally have a mild increase in their heart rate compared to normal controls. That is most likely related both to their epilepsy interictal abnormality in the autonomic nervous system and

djj

the anticonvulsants.

DR. WILKINSON: Dr. Deveraux?

DR. DEVERAUX: Just another question I'm kind of curious about with some of the information that's come out in recent years about lead difficulties with pacemakers, cardiac pacemakers. I realize that not many of these patients have been studied for long periods of time, but are there any issues that have come up in the longest-studied patients about lead difficulties? You mentioned an increase in impedance but about leads breaking and so forth? Any issues about that?

DR. DUFFELL: We had a very few lead breakages in the early pilot studies with the prototype devices, if you will, but there was a redesign of the lead which basically improved the welding of the ribbon portion to the end of the lead, and since that time, it's been my understanding--well, not my understanding; I know that we haven't had any reoccurrence of that kind of a design-related failure.

DR. WILKINSON: Yes, and then, we need to give the FDA presentation.

DR. SPENCER: I have a few questions. Looking at the efficacy, there seems to be a tremendous amount of variability between centers, and, in fact, it is my reading that seven or eight of these centers have not much efficacy.

djj

And in other centers, the efficacy seems to be very good. Is there any explanation for that, and have you investigated possible causes? I mean, we could enumerate a number of those. Do you have any insight into that?

DR. DUFFELL: It is a good observation. It is one I don't have a really good, clear answer for. It just so happens I have the best and the worst here in the room today as far as centers.

[Laughter.]

DR. DUFFELL: Maybe one way to address it would be to have Dr. Salinsky--I'm sorry, Marty, I know you're one of the best, but I wonder if you could address her question.

MR. KEELY: If we could speak directly into the microphones, the transcribers could pick up the questions easier.

DR. SALINSKY: I have the distinction of having the center with the worst results.

[Laughter.]

DR. SALINSKY: And my only explanation is I had eight patients studied at my site, and it is just simply a statistical oddity with small numbers of patients in a multicenter study that some centers will come out smelling like roses, and some centers will come out with very poor results.

djj

I was also involved in the E03 study, and if you look at the site-by-site data in the E03 study, I had one of the best profiles of results. Again, I think this is the fact that I had eight patients in that study as well, and with eight patients, anything can happen.

DR. SPENCER: A couple of more questions. There is some mention about withdrawal of the stimulation and the effects that it might have, suggesting, similar to drug treatment, that withdrawal might cause an exacerbation, a rebound effect. Has that been studied, and does it ever represent a danger? Can it represent predisposition to status epilepticus, for example?

DR. DUFFELL: No; we have no reported of either status or clustering of seizures occurring after discontinuation of stimulation, either due to intentional turning off the device or due to battery life depletion.

DR. SPENCER: So, the comments about rebound represent a minor degree, or was that investigated at all?

DR. DUFFELL: Actually, yes, we did do some look at rebound. The best studies, quite honestly, from a design standpoint for that were the early pilot trials, in which there were control periods applied after the device had been off, which the device was purposely cut off. Unfortunately, the E03 and E05 studies, by that time, since we knew enough

djj

about the functionality of the device, most of the investigators felt it was a bit unethical to ask someone who had had a response to cut it off, to basically do a challenge type trial. So, we haven't had any experiences in those population except where the battery has depleted.

But what we do see when the battery does deplete is that there is usually a gradual return of baseline value over a 2 to 3 week period, at which time, it will, you know, approach back to where the patient basically was before. But we have not, like I said, seen any occurrences of status or abrupt increase in seizure frequency as sometimes might be seen with an immediate withdrawal of an antiepileptic drug.

DR. SPENCER: Could you address the data that's available with regard to efficacy in adolescents? To my perusal, in the E03 and E05 studies, there are a total of 20 adolescents, of whom most received high levels of stimulation; is that the correct interpretation?

DR. DUFFELL: That's correct. Actually, I would like to call on maybe another one of my clinicians to address that. I think Chris DeGiorgio, and Chris, maybe you can address below 12 as well.

DR. DEGIORGIO: As far as the pediatric population, to date, there have been 65 children enrolled

djj

all together between the ages of 3 and 17 years of age. Forty-five enrolled in E04 and 20 in E05. I could put up these.

All together, there have been 21 in E04 who were less than 13 years of age, as young as 3 years of age. Overall, the mean age in the pediatric population was 12 years of age, again, the youngest being 3 and a half years of age. Thirty-one had either partial seizures or a mixture of partial and generalized tonic-clonic seizures; 14 had primary generalized epilepsy. There was a mean of 17 percent in the median reduction with 17 percent of that population, and 22 percent had a greater than 50 percent reduction in seizures.

For the E05 population, 20 children were implanted. There was a mean reduction in seizures of 26 percent in that population. Because of randomization, 16 were in the high group; four were in the low group. There was a significant increase in wellbeing and no deterioration of cognition in that population. In a within-group comparison, because the control group is too small, within-group comparison showed a highly significant reduction in seizures at the P less than 0.006 level in terms of the high treatment group.

In terms of safety, the most common adverse events

djj

were very similar to adults: 62 percent had hoarseness; 43 percent reported cough; 43 percent reported some nausea or vomiting. Only one death occurred in the children, pediatric population, a 16-year-old. It was not device-related. It was related to an aspiration which occurred after a seizure, a prolonged seizure.

So, overall, in the very young population, 21 children less than 13 years of age have been implanted. So, that means that 24 children in the adolescent range between 13 and 18 were implanted.

DR. SPENCER: And finally, with reference to the children, what quality of life outcome measure instruments did you use, and were they validated for an adolescent population?

DR. DEGIORGIO: Well, in the E05, we used the same measures, I believe, that we used in the adults, unless--so, there was no difference in the outcome measures in that group.

DR. SPENCER: Because those, I mean, most of the instruments you listed are not validated for use in adolescents.

DR. DEGIORGIO: That's correct.

DR. DUFFELL: Let me call on Anne Damiano, who is our expert in that area, and maybe she can address--

djj

MS. DAMIANO: Actually, you are correct. Some of them are not validated in an adolescent population. The SF-36, however, has been used in patient populations down to the age of 12.

DR. WILKINSON: All right; well, I think we really should go ahead and have the FDA presentation. There will be plenty of time for questions further.

Something pressing, Dr. Edmonson?

DR. EDMONSON: Just one basic question for the record, and I think I read that: the request for approval is for 12 and up, right? Is that correct?

DR. DUFFELL: That is correct.

DR. EDMONSON: Okay.

DR. WILKINSON: So, for the FDA presentation, Frank Lacy, I guess, is the first presentation.

MR. LACY: Good afternoon. My name is Frank Lacy. I am an electrical engineer. My presentation will highlight the nonclinical data in support of the safety and effectiveness of vagal nerve stimulation.

Three different animal models of chemically or electrically induced focal and generalized seizures showed a reduction in the number of seizures. In contrast to what the sponsor stated this morning, FDA does not believe that this reduction was specific to only the vagus nerve.

djj

Stimulation of C-fibers which was evidenced by a decrease in heart rate was necessary in the animals for effective vagus nerve stimulation and reducing seizures. As a result, in the clinical trials, the left vagus nerve was stimulated below the cardiac branch. Stimulation at this location has been shown to have less effects on cardiac function.

The mechanism of action is unknown. However, the literature does support that there were specific changes in the midbrain and brain stem.

Two safety studies were performed on rhesus monkeys, one involving a titanium cuff electrode and the other involving a platinum spiral electrode. There was no stimulation-related damage to the axons. There was also another study conducted on sheep, where the nerves of three sheep were removed and examined. The right nerve was used as a non-stimulated control, while the left vagus nerve was stimulated. The axons were found to be intact; however, there was epineural fibrosis as well as fatty infiltration in both nerves, and this was attributed to the presence of the electrode material and not due to stimulation.

However, mechanical damage caused compression of the axons, which was attributed to poor strain relief. Because of this surgical problem, the strain relief loop was placed close to the site of the electrode to relieve tension

djj

at the site of the nerve. Within the limits of the animal safety studies, the animal data supports the safety of vagus nerve stimulation.

The sponsor provides several safety features to guard against potential nerve damage. There are DC blocking capacitors in series with each lead of the stimulator to prevent overstimulation due to long pulse widths or short circuits.

The sponsor also provides a microprocessor within the implantable pulse generator to time out the amount of stimulation. Essentially, there is a watchdog code which is related to frequency and amount of stimulation in terms of time.

This is a graph of the watchdog organization, essentially, which is the code embedded in the microprocessor of the implantable pulse generator. The green area that you see here represents where no nerve damage occurred during the animal study. The red area that you see here represents where nerve damage occurred during the animal study, and then, finally, the blue area here represents the operating range of the Model 100-B generator, using version 3.8 of the software, and these areas are plotted for frequency of stimulation versus the amount of stimulation.

djj

Agnew and McCreary, as well as Bulora at the Huntington Medical Research Institute advised the sponsor on stimulus parameters that would be considered safe based on the animal data. The important thing to point out about this slide is that there is an inverse relationship between the frequency of stimulation and the amount of stimulation. The timer essentially will reset to zero output stimulus when the amount of time or the amount of stimulation has been exceeded. Irreversible chemical reactions due to charge injection can cause changes in the tissue or electrode, which can be avoided by limiting the charge densities.

Agnew and McCreary has set the limits for the charge densities for the anode and cathode respectively here as 167 and 250 microculons per cm_2 . The sponsor provides an electrode material of platinum with a surface area on the order of 0.07 cm^2 . The typical charge densities that the sponsor uses or stimulates with are well below the limits established by Agnew and McCreary. This is important, because this limits the effect or the pH change in the tissue that surrounds the electrode.

The maximum current supplied to the nerve is 15 milliamps. This is related to the maximum voltage and the lowest lead impedance, which are 12 volts and 800 ohms

djj

respectively. This is within the guidelines established by the American Association of Medical Instrumentation or AAMI guidelines for implantable peripheral nerve stimulators.

Typical lead impedances once the physician turns the stimulator on are on the order of 3 kilohms to 5 kilohms. This lead impedance remains relatively constant after the physician turns the stimulator on. This yields currents supplied to the nerve on the order of 2.4 to 4 milliamps and, again, referring to the last slide, this results in charge per phase as well as charge densities within the data accrued by Agnew and McCreary.

And then, finally, the sponsor provides labelling to the physician in order to increment the output stimulus via the programming wand and the computer.

I would like to thank Steve Tertel for helping Dr. Costello and myself with the slides and present Dr. Costello, who will present the findings from the clinical data. Thank you.

DR. COSTELLO: Good afternoon, Dr. Wilkinson and members of the panel. This afternoon, I will be discussing issues regarding the safety and effectiveness of the vagus nerve stimulation device.

The proposed indication for the NCP system is that it would be used for the reduction of seizures in adults and

djj

adolescents over the age of 12. It would be an adjunctive therapy. Up to three antiepileptic drug medications would be used in patients with partial onset seizures, with or without secondary generalization.

The issues which FDA has regarding the safety and effectiveness are summarized on this slide. It is hoped that the panel will advise FDA on the clinical impact of these issues. As the sponsor has already stated, there are five clinical trials of the NCP system. The E01 and E02 studies were pilot studies. I will be focusing primarily on the E03, E04 and E05 studies, which were the large, multi-center trials. The E03 and E05 trials were randomized, controlled trials. However, the E03 study was amended to enroll up to 200 patients. As you can see, when the PMA was submitted, only 115 patients had actually been stimulated with the device.

As a result of this, as well as other protocol deviations, the sponsor was asked to perform a confirmatory study, which was the E05 study. The E04 study was an open-labelled study which had much broader inclusion and exclusion criteria, thus allowing vagus nerve stimulation to be brought to a larger amount of the epilepsy population.

The first issue to be discussed is what is the best primary effectiveness measure or measures to be used in

djj

evaluating the vagus nerve stimulation system. There are three primary effectiveness measures, either the median percent change in seizure frequency, the mean percent change in seizure frequency or the number of patients who had received 50 percent or greater response. Either one or all of these measures were used in the E03 through E05 studies.

This slide demonstrates the change in seizure frequency for the E05 study. As the sponsor has stated this morning, the high group were patients who were stimulated using stimulation parameters that were expected to result in optimal seizure reduction. However, the low group were stimulated at parameters which caused sensation but was not expected to result in optimal seizure reduction.

As can be seen, the median percent change for both the high and the low groups were approximately 20 percent. In both the high and the low group, there were patients who were very good responders, becoming essentially seizure-free, as well as patients who were poor responders, having 100 percent or greater increase in their seizure frequency.

FDA has examined both individual and group characteristics of these patients in an attempt to predict who would be either good or bad responders. We were unable to find any individual or group characteristics that would

djj

predict success or failure.

The effectiveness results are shown in this table. The values are presented for the high and the low group in both the E03 and E05 randomized controlled trials. In contrast, the open-label E04 trial, where patients were all stimulated at optimal stimulation parameters, has only one value. In the E03 study, the mean percent change, the median percent change and the number of patients who had greater than a 50 percent response were all statistically significantly improved. However, the P value is not corrected for the two interim analyses which had been performed on the stater.

In contrast, the E05 study had a statistically significant change only in the mean percent change. The median percent change and the number of patients who had greater than a 50 percent response was not statistically significantly different between the high and the low groups.

In addition, the E03 study stimulated patients every 90 minutes, as compared to the E05 study, where patients were stimulated every 180 minutes. The sponsor this morning has discussed reasons why the E03 group potentially was so low, and using the inclusion/exclusion criteria of the E05 study, did result in approximately a 15 percent reduction. However, if you examine this data from a

djj

type of dose-response in terms of 90 minutes versus 180 minutes, we would still expect a lower value in the E05 group relative to the E03 group.

In terms of the open-label E04 study, the mean percent change was not significantly different. It was only a 7 percent change, while the median percent change and the greater than 50 percent responder rate was statistically improved.

These are secondary endpoints which were examined during the E05 study. Both the within-group analysis for the high and the low group, the comparison of the stimulation to baseline, were statistically significantly improved. However, other secondary endpoints, the number of seizure-free days, the number of days between seizures, seizure intensity and duration, were not significantly improved. In terms of global evaluations, there was a statistically significant difference between the high and the low groups as rated by the patient and the investigator. In terms of the within-group analysis, all three evaluators considered the patients significantly improved with stimulation.

These were some of our other quality of life measures that were performed during the E05 study. Although some of the individual tests in these measures were

djj

statistically significantly improved, as would be expected by chance, the overall tests did not show a statistical significance between the two groups.

The next issue which I would like to address is the long-term data. As can be seen in the extension phase of the XE5 study, here are the results of the randomized, controlled trial and then followup at 4, 6 and 9 months. Both the mean percent change and the median percent change during the extension phase showed approximately a 30 percent seizure reduction for these patients. However, this data is confounded by the fact that the patients were changing their medications during this period.

Similarly, despite optimal antiepileptic drug therapy, only 20 percent of the patients in the extension phase, using a last visit carried forward analysis, had 50 percent or greater reduction in seizures. One-third of the patients had some type of an increase in seizures, with 17 percent having greater than a 25 percent increase.

The final issue which FDA would like to discuss is the safety issue. The safety issues will be discussed in three categories: serious adverse events; the issue of increased seizures and the issue of SUDEP, or sudden, unexpected death in epilepsy. This slide summarizes the patients who dropped out of the E03, E04 and E05 studies. I

djj

do want to mention that the question was raised this morning regarding sympathetic activity. Although there were no cardiac or respiratory events measured by Holter monitoring or pulmonary function tests, patients did significantly complain of dyspnea during stimulation.

In terms of the E03, E04 and E05 studies, one patient in the E05 study dropped out due to a left hemidiaphragm paralysis. It is thought that this is due to an anatomical anomaly in the area of the vagus nerve. One patient in the E03 study dropped out due to left vocal cord paralysis. This was due to a generator malfunction which has since been corrected, and this adverse event has not reoccurred. One patient suffered a myocardial infarction and decided to withdraw from the study.

In terms of the patients who are followed from the acute phase, which would be 3 or 4 months, depending on whether it was the E03, E04 or E05--E03 and E05, the acute phase was 3 months, and E04 it was 4 months to 1 year--five patients died. It is important to realize that one patient did die of aspiration pneumonia, and there is a warning proposed regarding aspiration for this device. And six patients dropped out due to lack of efficacy. It is important to realize that 95 percent of the patients continue to use vagus nerve stimulation at the end of 1

djj

year. Eighty-two percent are using it at the end of 2 years, and 69 percent are using vagus nerve stimulation at the end of 3 years.

This slide shows each of the studies and the percent seizure increase. As you can see, in each of the studies, there were patients who had greater than a 100 percent increase. In the E05 study, the range went up to a 234 percent increase, while in the E04 study, it went even higher, to a 680 percent maximum range.

This slide summarizes the 17 deaths that are known to have occurred in patients having a vagus nerve stimulator implanted. This includes all of the patients in the clinical trials as well as patients who have the device outside of the US, where it is in commercial use. Again, note the one patient who did die of aspiration pneumonia. As of June 1, when this slide was made up, there were four SUDEP deaths, three probable SUDEP deaths and three possible SUDEP deaths. The sponsor has since provided evidence that one of the SUDEP deaths was actually a possible SUDEP death. In addition, two patients died of accidental drowning.

This slide shows a comparison rate of various studies in epilepsy populations comparing the SUDEP rate to that found with the Cyberonics device. I would like to bring your attention primarily to the Lamotrigine and

djj

Gabapentin clinical trials, drugs which have recently approved for partial onset seizures by drugs. The value of 4.2 is quite in line with that found in the Gabapentin study. This value is for definite and probable SUDEP rates. When the possible SUDEP rates are added in, the ratio is 6.1. If you do include the two drownings, the ratio rises to 7.3. In summary, possible SUDEP does increase the SUDEP rate with the Cyberonics device.

In summary, effectiveness in the confirmatory E05 study was found when the mean percent change was used as the primary determinant of effectiveness. However, using the E04 study, the mean percent change was not statistically significantly different. In terms of the safety, there are patients who have large increases in seizure frequency, and we are at this point unable to predict which patients these will be. The mortality rate for the study was 10.4, and the SUDEP rate for definite and probable is 4.2.

Thank you very much. Are there any questions for either Mr. Lacy or myself?

DR. WILKINSON: Yes, Dr. Piantadosi is first.

DR. PIANTADOSI: Thank you.

I'm still a little worried about the death rates that we are seeing. Are the figures that you presented us essentially identical to those that we saw earlier? Or have

djj

these been adjusted for severity of disease and age?

DR. COSTELLO: No, they have not been adjusted for severity of disease or age. There is some discrepancy in terms of the numbers that were presented this morning. I used a different numerator. It was a more recent of 1,635 years. The firm had computed a SUDEP rate of 4.5, based on 1,335 years. One of the sponsor's investigators did mention today that the level was even lower; however, this data has not been provided to FDA.

DR. PIANTADOSI: If we were being very conservative here, and we took your last line, which are definite, probables and possible, including the drownings, which, to my naivete, would seem appropriate to include, then, the 7.3 is one of the highest rates in the series that you showed a moment ago, recognizing the fact that there are some difficulties in comparing these rates because of the differences in severity of disease.

Are you concerned by that? Should we be concerned by that?

DR. COSTELLO: Comparing it to the Lamotrigene trial, it is higher, and I am concerned regarding the comparison to the Lamotrigene trial. However, these are patients who are refractory to many medications; who are severe patients, who do not even have the option of surgery,

djj

and I am not familiar with the patient population that was used for the Lamotrigene and Gabapentin trials. So, they may, in fact, be a much less severe population, and when you compare the data to Nashef, which was surgical candidates for epilepsy, it is lower than his number of 9.3.

DR. PIANTADOSI: Yes; well, one of the things that's concerning me is that the endpoint being measured in all of these studies is, in some sense, a surrogate, counting the number of seizures. I realize that to the patient and to others, it is a very important endpoint, but it may not be as definitive as some other things that we could measure. And there are numerous examples in the methodologic literature about the weaknesses of accepting clinical trial data based on surrogate outcomes, and I would point to, as a recent and a very dramatic example, the cardiac arrhythmia suppression trial, in which the study was designed and the endpoint was selected on the basis of looking at arrhythmias and suppressing them with a drug.

And the studies originally seemed to show that the drug was effective in suppressing arrhythmias. The problem was that it was so good in suppressing arrhythmias that it was killing people, and the mechanism was not understood until much later and wasn't even believed until the results of the randomized trial.

djj

So, I am very nervous when I see high mortality rates associated with a supposed benefit, even though we don't have a way biologically right now to connect the two. So, that is why I have harped on this this morning and why I am still very nervous with this high death rate. What's your sense of that? I mean, I'm struggling to get some reassurance that my concerns are not well-founded.

DR. COSTELLO: I really can't say anything more than what I said regarding the surgical candidates. Maybe Dr. Duffell would like to discuss it.

DR. DUFFELL: Thank you, Dr. Costello. I really think it would be probably inappropriate for me to comment on it, since I've got two experts here, one of whom, I know, actually worked on the Lamotrigene paper. Maybe I could call Dr. Annegers and Dr. Hauser both up to comment on I think what's most important here is that we make sure that the rates that we're reporting on here are apples to apples from a comparison standpoint, and maybe they can go into that and also speak about standardized mortality ratios as well.

DR. ANNEGERS: Shawn, could I have some help with the projector?

Fred Annegers again from Houston. Let me try to give some background. First of all, I think it's important

djj

to point out that in all of the recent trials of the new epilepsy drugs, this phenomenon of SUDEP has arisen, that there appeared to be an increased appearance of sudden, unexplained, unexpected death in individuals with intractable, complex epilepsy. Normally, they are found dead in bed is the most common situation, and this has been a subject that has been debated in the epilepsy literature: to what extent is this a real phenomenon related to epilepsy and the severity of epilepsy.

But because of the increased incidence in all of these recent trials, a panel was put together by the FDA and then Burroughs-Wellcome to evaluate the deaths in the Lamotrigine trials. Myself, Dr. Litsma, a neuropathologist from Chicago, and four others were assembled to put together criteria for SUDEP and to evaluate the deaths in the Lamotrigene trial and try to decide whether or not it was elevated and whether or not it was related to the drug.

And the definition that we produced, although it was done, I believe, in 1993, was not actually published until Epilepsy of this January, but it's available in an article with Litsma as a first author. I won't go over the definitions unless we need to, but these were the definitions for SUDEP, mostly on the circumstances. One problem is we needed a working definition that would deal

djj

with the highly variable information available on circumstances of death and whether or not autopsy was available.

So, SUDEP is generally put into three categories. One would be definite, where the circumstances of the death meet the criteria and autopsy is available. Probable would be where the circumstances of the death fit the criteria, but autopsy is unavailable. Possible would be where there is a competing explanation, but SUDEP is considered possible, and then, others would be considered not SUDEP.

This is from our report that you had that was based on the experience. I think the reason for the slightly different numbers is that we were using for our report that went with the submission a cutoff date of August 15, 1996, which included a certain number of person years and 15 deaths at that time, and taking the probable possible, we had 4.5, and here, we did a comparison with the other trials. Again, I want to stress you don't want to compare these directly, because these rates are not adjusted even for age, let alone severity of seizure, but the point is they are in approximately the same range.

I want to address the drowning issue, because I think there has been some concern there. It's long been known that drowning is a major problem with epilepsy, and,

djj

of course, a seizure-related death due to drowning, which might be due to a seizure while swimming or a seizure causing submersion, neither of those are considered SUDEP in any of the studies that I've been on. In the study that we did of the 15 deaths, three had drowning. The two that were mentioned before, we all thought had an obvious non-SUDEP explanation. One was an observed seizure while swimming in the Red Sea, and the other was a case where there was an injury and, I think, a fall into a pool found submerged, and the autopsy was consistent with drowning. So, neither of those were considered SUDEP.

A third death from the United Kingdom found dead with head in bath in the bathroom was a very difficult one, and we had that one in the possible category.

So, this is just the conclusions that you already have, that we used the same methods as in the Lamotrigene study and some of the other recent SUDEP studies that Dr. Litsma, Dr. Hauser and I have been involved in. We do feel, and, as I was asked before, that probably, this cohort is weighted at least to some degree towards higher risk, and if appropriate adjustment could be made, would probably be more like the overall rate of the other recent drugs, although I can't do that now with information available.

And in comparing to surgical series, we feel that

djj

this cohort is similar to what we would expect, given the nature of the patients, rather than related to the device. On the last one I show, we do have an update now using the new deaths that Dr. Costello mentioned. There have been two deaths that we're aware of since we did our study August 15, 1996, and during that time, there have been approximately 667 patient years. The two deaths are both from the UK. Both might be SUDEP, but I wouldn't want to try to classify at this time because I think it should be done through the same review and adjudication as we did on the others, but even if we assume for now they're both SUDEP, it would mean the interval rate of definite plus probable SUDEP since 10 months ago would be 3 per 1,000. So, the two that we have had since then would be the 3 per 1,000. I think somebody said it was less, and less only meant in the interval rate.

If we now take the total experience of the 2,000 person years of observation through the present, the SUDEP rate of definite plus probable would be 4 per 1,000 person years.

DR. DUFFELL: Thank you.

Dr. Annegers walked us through the numbers. I would like, maybe, Dr. Hauser to kind of close it with a clinical perspective on what these numbers mean to the practicing neurologist as far as interpreting this for

djj

patient information.

DR. HAUSER: Yes; I am Alan Hauser; I am on the scientific advisory board for Cyberonics, and my way has been paid here. I have no other financial commitment or obligations or recipient from the company.

I would just like to stress that in terms of the questions of the submersion deaths or drownings, at this point, the British studies, the studies which are being done in Great Britain and the studies which have been done in this country with patients worldwide, for instance, the Lamotrigene study would not have included as cases these submersion deaths. We know that there were some cases in these comparison groups who had drowned. I don't know how many there were, but I think for appropriate comparison, and granted, we can't do this by age, by severity and other things, but I think for appropriate comparison, we should not include at this point submersion deaths or deaths by drowning.

I feel myself that the frequency that we're seeing of sudden death within this cohort is similar to that which has been reported both from the drug trials with severe cases and done in patients with relatively similar age limitations, although we can't say that the age distribution of the cases are similar. And I think it certainly is

djj

consistent with and actually a bit less than the studies that have looked at the frequency of sudden, unexpected death in surgical series, the people being evaluated for surgery and surgery failures.

I guess my bottom line is I don't think that the sudden death is an issue specific to the device. It's a specific issue in terms of people with bad epilepsy.

DR. COSTELLO: I also have just one other comment. In your packets that you received, there was a consult from drugs regarding the issue of SUDEP, and in terms of the definite and probable SUDEP rates, the drug people felt it was totally in line with the recent Neurotin clinical trials.

DR. SPYKER: That's on the top of page 29, 4-29. This is the same team that Greg Burkhart and John Feeney worked on, Lamotrigene, in fact. And perhaps as important is that they sent us the labelling for Lamotrigene. On the bottom of page 10, the last few lines on page 1-10, is the SUDEP language that they crafted--it sounds like some of the folks here helped with that--for the labelling, and I would expect that if this drug comes for approval, we will do something along those lines.

DR. PIANTADOSI: Could I just ask the FDA very directly--I'm not confused about what the company thinks,

djj

and I really am not interested in the nuances of how SUDEP is defined. Is the FDA satisfied that this device is not associated with an elevated risk of death, all-cause mortality, whatever you want?

DR. COSTELLO: I believe that, based on the data which we've gotten in terms of, like, Holter monitoring effects, cardiac effects, that there had been no patients except for that one who had a myocardial infarct, there have been no patients who have died of myocardial ischemia, which would be one of the things which I would be concerned about with stimulation of the vagus nerve. So, I believe that the death rate should be compared to that in the drug trials, and I am aware, as I had said previously, that the drug trials do use less severe patients.

So, to answer your question, I don't believe it has been shown that the high death rate is directly related to the device. However, we only have 2,000 patient years of experience and a limited number of patients. At the request of FDA, the firm was very responsible in terms of looking at the SUDEP rate. I think--I could be wrong--that there were like seven SUDEPs in the United States, and we said to the firm, well, this is not a very large population; will you go out and look at the commercial population? And they tried to contact every single patient outside the United States

djj

who has used this device, and they were able to come back with data on all of the patients, I believe, except for the patients in Australia, which were six.

And again, as you heard this morning, the device has not been taken off the market in Europe for any reasons related to safety, and in the limited experience, then, that we have, I cannot say that I believe that there is an increased risk right now, but I would not want to rule it out either. I think that would require a longer-term study.

DR. WILKINSON: Dr. Nuwer, you were next.

DR. NUWER: Yes; I thought that the question to Dr. Hauser and Annegers was also along the lines of whether there was a difference in the inclusion/exclusion criteria, comparing this study to Lamotrigene's study or the Gabapentin study, and I didn't think I got a clear answer to whether or not there was a difference in the patient category, although there was an allusion to that at one point.

DR. COSTELLO: Doctor?

DR. HAUSER: For the E03 study, I think there would be no differences in inclusion or exclusion. My feeling, though, is that the relatively high proportion of people who had had surgery, that is, about 15 or 20 people in the E03 study, is probably higher than that in the other

djj

studies. I can't say exactly what the frequency of surgical failures are in the other drug studies.

The E05 study, which, in fact, has, from our followup data, has a somewhat lower rate than the earlier studies, if we assume that these later cases have really come from the E05 study, differed only in that we excluded individuals who had had failed surgery. They were not included in the recruitment strategies, and if these people are specifically at higher risks, which they may be, then, there might be some minor differences. But I can't really count on that, because again, we don't have access to that information from the drug studies. We do have comparisons with population data, and, as I said, we do have, I think, reasonable comparisons with what we expect, particularly among the surgical failures. And I think it is clear that the frequency, at least for SUDEP, is lower.

All cause mortality, again, is about what has been reported from cases series with severe epilepsy, prevalent series. But I think it is comparable, and I think as much as we can do at this point, the comparisons are reasonable, and it does not appear to be in excess at this point. In fact, I think it's reassuring that the frequency is lower and, I think, much more in line with the drug studies which were performed on Lamotrigene and, for that matter, all of

djj

the recent drug studies have had this as a problem, not just Lamotrigene but also Gabapentin and, I guess, Tipiramate, there has also been a question; so, it's consistent.

DR. WILKINSON: Dr. Edmonson?

DR. EDMONSON: I gather that most SUDEP cases occur during sleep; isn't that true, that the vast majority of SUDEPs occur during sleep?

DR. COSTELLO: I believe that was true.

DR. EDMONSON: Okay; I was just wondering how many patients were actually studied by a Holter monitor. All of the patients in the E05 study?

DR. COSTELLO: Correct; all patients in the E05 study had Holter monitoring during baseline and at their followup visits.

DR. EDMONSON: Okay; and another question, and this is probably more a reflection of my naivete about electronics, but for Frank Lacy, when the generator is on the agonal downturn of battery life, I would imagine that the risk of more erratic stimulation parameters and output would occur. Is there any data at all concerning looking at discharges, pattern of output on the agonal phase of the generation, the life of the generator?

MR. LACY: Could you possibly rephrase that? I'm not sure I understand the question.

djj

DR. EDMONSON: Okay; batteries going dead.

MR. LACY: Yes.

DR. EDMONSON: I imagine that especially after having had this commercially available outside the U.S. that the experience of folks using it would sort of dictate when to change the generator, and I was wondering really if there is any data, experimentally or animal models or in the outside the U.S. experience that would tell us whether or not, when the battery is beginning to phase out, whether or not there are erratic discharges or whether or not all of those stimulation parameters, whether or not a lot of those change. Is the integrity still there, but the juice is low?

MR. LACY: I have several comments on that, and maybe the sponsor can add to it. The labelling advises the patient to use the magnet to test the output of the stimulator daily for battery life. There is a DC-DC converter within the pulse generator that essentially increments or steps up the battery voltage, so that it is usable for--I think the shelf life is on the order of 3 years, and the sponsor has indicated that their further plans are to put an end of service indicator on the device, but there is not one as of yet. I don't know if they have anything to add to that.

DR. DUFFELL: Yes; if it is okay with the panel,

djj

one of our engineers might could add a little bit to what Frank said, but he's basically correct.

MR. ADKINS: My name is Alan Adkins. I'm the director of engineering for Cyberonics.

In the end of life, it does go through when the battery at a particular point, it will go through erratic stimulation. The erratic stimulation is always at an amplitude--because the batteries are very weak--it is always at an amplitude that is less than the programmed amplitude, and it is only for a very short period of time.

DR. EDMONSON: So, based on that experience in doing the diagnostics to determine when to replace it, have you a recommendation about what sort of parameters would indicate that it is timely to or would be useful to be preemptive and replace it? What point?

DR. DUFFELL: I'm not sure I understand completely your question, but it sounds like you're asking something about like an end of service type indicator of sorts.

DR. EDMONSON: Right.

DR. DUFFELL: And presently, the device does not have that characteristic in it. There are obviously a lot of evolutionary changes that we would like to see to the device subsequent to an approval. Those would certainly be one, and, in fact, we have already got an algorithm that

djj

we've worked on. But for purposes of trying to keep everything status quo during the clinical trials, keep the device exactly the same so we are again comparing apples to apples, we haven't implemented those things.

DR. EDMONSON: Okay; but as a product of collective experience, you guys must have some idea about, you know, when end of service is indicated; when it should be replaced, at what stimulation frequency would you recommend it's time to get a new generator.

DR. DUFFELL: What we would refer to presently is the physician manual, the labelling that occurs in the back, and there is a chart that basically allows the physician to say if I'm treating at these nominal values, at these levels, I can expect a life of approximately, and at that point, of course, during that time interval, the patient would be warned be on the lookout type thing. Certainly, it would be in the clinic charts during those periods to evaluate.

Also, most importantly, remember one of the reasons that we have the magnet is because the instructions are to the patient to test the functionality of the device daily, so that if a device did go dead sometime, and they weren't aware of it, because oftentimes, as we have heard, patients do accommodate to the effects of stimulation, so it

djj

is not always as obvious as, perhaps, some of the patients that we have seen here today. So, if they are doing that daily, they should know when the device is no longer functioning and should, of course, appropriately arrange to come in and see their physician.

DR. SPYKER: Page 2-25 of the pack has the battery life table that he referred to. A nice big one.

DR. EDMONSON: Okay; so, the dropoff can be rather fast; once it starts to go bad, it's a dropoff.

DR. DUFFELL: That is correct, yes.

DR. WILKINSON: Dr. Snead, I think you had your hand up.

DR. SNEAD: Yes; I have a question for Dr. Costello and a question for Mr. Lacy.

Do you know what the incidence of generator malfunction was over all of these patients?

DR. COSTELLO: I'm sorry; I don't know that offhand. I know it was very small, though. I would say on the order of probably two or three patients out of the 400 that have used the device in the clinical trials; quite small. It hasn't, at least, come to light as a major problem.

DR. SNEAD: In regard to the deaths, have you looked at the deaths in relation to high versus low

djj

stimulation or in relation to use of the magnet? Or is there data available?

DR. COSTELLO: We have looked at the deaths in terms of the high versus the low. We can go back and determine which patient was on high versus low, but at this point, I don't believe there is enough data to come to a conclusion regarding that. And in terms of the magnet, we have not looked at that data.

Do you have any further comment in terms of the high versus the low SUDEP rate in patients?

MR. TARVER: Brent Tarver, Cyberonics. None of the patients were on low stimulation. None of the patients died in the acute portion of the study. It was only add-on time.

DR. COSTELLO: So, in other words, they were all receiving optimal stimulation parameters at the time of death.

DR. SNEAD: Does that change the opinion of Doctors Hauser and Annegers in terms of the significance? Isn't that significant that only the patients on high stimulation--

DR. ANNEGERS: Yes; we didn't calculate the person time actually on high versus low stimulation during the trial phase, but that was quite brief, only 3 weeks per

djj

patient--I mean 3 months per patient. We did look at the deaths in terms of their temporal association with implantation and found the incidence to be very similar when we stratified the time periods.

MR. TARVER: I'm sorry; I'm just going to say: there is only about a total of 40 patient-years on low stimulation total, because it's just during the acute portion of the study.

DR. WILKINSON: Dr. Piantadosi, you had your hand up?

DR. PIANTADOSI: Yes, I had a different question, but that has prompted me again to think about this issue. Do we have any sense as to the duration of epilepsy in patients prior to their participation in the trial and receiving the implant?

DR. COSTELLO: I believe the firm showed a slide this morning.

Do you have that slide available, or would you just like to know? I guess it's easier.

DR. DUFFELL: Yes; I'll just quote you the number, yes, because finding the slide again might be difficult. On average, they had about 22, I think, 22.3 years.

DR. PIANTADOSI: On average.

DR. DUFFELL: yes.

djj

DR. PIANTADOSI: So, you have patients who have had a very longstanding experience with their disease. You implant this device in them, and then, you have events following that implantation--

DR. DUFFELL: Yes.

DR. PIANTADOSI: --in the population. I just want to be sure I understand--

DR. DUFFELL: Yes.

DR. PIANTADOSI: --what's going on.

I have a question for the FDA. You alluded in your presentation to the lack of controls over medications during the long-term portion of the study, and I presume from looking at the protocol that there were no built-in controls on ancillary treatments in the evaluation period immediately following implantation; is that correct?

DR. COSTELLO: That's correct. They had to keep their medications constant during the screening phase and then for the 3 months of the acute study. In the E04 study, there was no control over medications required, and in the extension phase, all patients could adjust their medication to receive optimal seizure reduction.

DR. PIANTADOSI: Do we have any way to understand or get information about whether or not there were influential medication changes during the study period that

djj

might have affected the evaluation of outcomes?

DR. COSTELLO: We have looked. The patients were on numerous antiepileptic drug medications. I think, actually, in your handout, in the E05 trial, there may be a table.

DR. SPYKER: Page 5-16; section 5, page 16.

DR. COSTELLO: I'm sorry, of the drugs that these patients were on. We had asked the sponsor to do an analysis to see if the device worked better in conjunction with certain drugs, and we were unable to find any type of relationship.

DR. PIANTADOSI: Those were baseline values, though, were they not?

DR. COSTELLO: No, these--

DR. SPYKER: This is drug levels by visit. The table gives the drug levels for all of the drugs by visit.

DR. COSTELLO: And the other thing is the possibility was raised that drug levels may be changed during the vagus nerve stimulation due to vagal effects on the intestines, and that was not found.

DR. PIANTADOSI: My last question relates to the definition of baseline, which seems to have been defined for these studies prior to the implantation. Why is that? Why would it be defined then rather than for the period of time

djj

immediately following implantation?

DR. COSTELLO: Basically, that was the way it was set up. They came in; they kept on their constant dose for 3 months, because the purpose was to compare. The firm originally, in the E01, E02 studies, had done a nonrandomized control trial, and we were concerned about changes in medication-causing effects. So, therefore, we asked them to randomize to the high and the low groups. Therefore, I think it would be very difficult. You have to have the baseline. You would have the baseline, the 3-month baseline, and then, you would compare the high and then the extension optimal. You wouldn't expect to see that much of a change following the high stimulation. And actually, that's what happened. They did increase slightly during extension, and the low group did catch up to the high group.

DR. PIANTADOSI: Well, that's one of the features that concerned me. When you look at the temporal trends in the responses, the period surrounding the implantation seemed to be consistently higher than that immediately before, and I just wondered to what extent that issue had been discussed in the agency.

DR. COSTELLO: Basically, they had a 2-week recovery following the surgery, so that any surgical impact would hopefully have worn off by then. But outside of that,

djj

we have not looked at it any further.

DR. WILKINSON: Other questions from this side of the panel?

[No response.]

DR. WILKINSON: I had two questions, one for Mr. Lacy.

MR. LACY: Yes.

DR. WILKINSON: MRI safety, obviously, a lot of these patients with epilepsy are likely to be subjected to MRI scans. So, I am not clear what studies were done of MRI safety. I know the recommendations differ for body coil and head coil. What studies were done?

MR. LACY: I think Dr. Munzner is in the room and can best speak on that. He was the reviewer for the MRI compatibility.

DR. WILKINSON: And was there an effect of the MRI on nerve damage or on damage to the device?

DR. MUNZNER: Robert Munzner. I assisted in the review, but I did not prepare this part of it for presentation. There was considerable data presented by the company concerning MRI safety. As you know, MRI has a number of different phenomena associated with it. We are all familiar with the huge magnet that goes with it. That was not a problem. There is also a large pulsed magnetic

djj

field which does induce a brief current pulse on the wire. That was not judged to be a problem, although there was a potential possibility of some nerve stimulation occurring, but it would be very small.

Where the problem does come is with the radio frequency field at 60 megahertz. This has a potential for inducing heat into the leads, and, in fact, in a phantom, there were measurements made of the temperature rise in the leads, and it was more than significant. It was dangerous when used with body coils. So, the device can't be used with whole body scanning, because you can expect the leads to become hot and to cause injury.

Using field coils, the RF energy is not coupled well to the leads kept around the head, and in this case, there was no significant temperature rise in the leads and judged to be quite safe under the conditions of tests, which is 1.5 test, if I recall correctly. That has significance not because of the magnetic field but because of the corresponding radio frequency part of the spectrum that's used. As the magnet size would increase with a different machine, then, you would expect, in fact, would require a higher RF frequency. The higher RF frequency will deliver more energy but roughly in proportion to the frequency, so that an extrapolation of 1.5 to 2 was made by the company

djj

based on the data they had as an estimate of where they could assure safety, and that appeared to us to be correct.

DR. WILKINSON: So, the question of damage to the device itself, the device itself is not damaged by the magnet or by the collapsing RF currents, et cetera. I noticed it does reset the device, or it may reset the device, but it doesn't damage the device.

DR. MUNZNER: That's right. You can expect the magnetic field to perturb the magnetic detection device in it, the read switches. That's a given. And so, it has to be reprogrammed afterwards, but there was no indication that the device would be made nonfunctional.

DR. WILKINSON: One other question, then, for Dr. Costello: there seems to be some 17 percent of patients, if I followed your analysis correctly, in whom seizure frequency increased, and yet, only one patient dropped out because of increased seizures, and six dropped out because of lack of efficacy. Are these people asking for trouble or what?

DR. COSTELLO: Well, one person dropped out during the Q phase for lack of efficacy, and I believe there were six that had dropped out from the E03, 4 and 5 due to lack of efficacy up to 1 year. That patients apparently, 95 percent of the patients in the E01 through E05 studies were

djj

continuing at 1 year, so, they must feel they were getting some type of benefit. I do not have a plot, for example, of exactly the percent increase in seizures versus the ones who did drop out due to lack of efficacy.

Do any of the clinicians have any comments?

Dr. Salinsky?

DR. SALINSKY: I'm not sure if this directly answers your question, but it might answer your question. This is last visit carried forward data from the E03 study. I think the open extension trial data, of course, is uncontrolled data, and in order to make it as good as possible, we took a look at the E03 group, for whom we had the longest experience, and we did a last visit carried forward analysis. So, out of 114 patients who were in that trial, at 1 year of high level stimulation, 100 patients were still going. That was about 88 percent. And as far as the other 14 patients go, we kept their seizure rates at wherever they were at when the patient dropped out of the study. Most of the 14 patients that dropped out dropped out somewhere along the way because they felt that they were not benefitting particularly from vagus nerve stimulation. We kept that seizure rate and just carried it along so as to, if anything, bias the results toward a negative result. So, this is a very conservative analysis.

djj

And the major reason why patients dropped out during that 1-year followup was a perceived lack of efficacy. That was in E03. This is the results of the last visit carried forward analysis, showing that if you go out in 3-month blocks, 3 months, 6 months, 9 months, 12 months, at the end of 1 year, there appears to be a trend toward continued improvement of seizure frequency. There is not a statistically significant difference between the first 3-month block and the last 3-month block, but the trend is in the direction of further improvement of seizure control. Furthermore, we did, in an attempt to make this data even better, take a look at medication changes, because we did have complete medication data on the 100 patients who continued throughout 1 year, and the medication data showed that there were more patients who decreased the number of medications they were using than increased the number of medications that they were using.

DR. WILKINSON: Were there patients who initially had an increase in the number of seizures, presumably not a 680 percent increase, but were there patients who had an initial increase in number of seizures and, over time, found that their numbers decreased below baseline?

DR. SALINSKY: I do not have that data.

DR. WILKINSON: It's just puzzling, if a lot of

djj

patients were having more seizures, why they would continue to use the device.

DR. COSTELLO: I would just like to make one comment, though. At the beginning of the E05 protocol, we had suggested to the firm that they look at decrease in medication usage as more of an objective type of outcome, and the sponsor decided against measuring medication and using that as an endpoint of their study.

DR. WILKINSON: But it could be a confounding variable: patients felt better with lower medications and were therefore willing to accept more seizures.

DR. DUFFELL: Dr. Basim Uthman has a slightly different perspective on the same question you are asking about, why these patients will continue treatment; if I could have him address you as well.

DR. UTHMAN: I'm Basim Uthman, and I have seen these patients since March 21, 1989. That is my first patient. Over 8 years, there were some patients who did not have significant reduction in seizure numbers or frequency, and because it was a long period of time, 8 years, obviously, they had to reach times when the device had reached end of life, the battery had reached end of life, and they needed to change. And then, I stopped and looked at the numbers and talked to the patient and said why do you

djj

want to have this procedure done again? And your numbers show that there is no significant reduction.

And traditionally, as we have been taught, over time, that a significant reduction in the number of seizures is more than 50 percent reduction in seizures. Although some patients do not agree with that, because I have got some patients who had a 70 percent reduction in seizures, and at the time when the battery reached end of life, they decided not to replace it, because their expectation was we wanted to have complete seizure control. So, that is on one hand.

On the other hand, there were patients who did not have any significant change or reduction in seizures, but yet, they were begging for replacement of the device. And three things have been reported. One is decreased duration of seizures; two, decreased intensity of seizures and the third, we are snapping out of it much faster, so, there is a reduction in the postictal state. In none of these parameters, I could comment in a scientific fashion, because I could not measure this short of monitoring them with a monitoring unit.

But in the E05 study, in my patient population, which is 15, I had nine who reported improved quality of life. Only three of them had more than a 50 percent

djj

reduction in seizures. So, there are other components that patients perceive as an improvement that we are not measuring for in our current studies, and that is not a criticism to how we studied these things, but maybe it's something we need to look at later on.

In fact, seven out of the 15 patients had a decrease in either duration or intensity of seizures. One of the seven had a decreased intensity. Three had a decrease in duration alone, and three had a decrease in both duration and intensity.

DR. DUFFELL: And one last remark, too: dealing with seizure types, because he was talking about an increase in seizures, but we need to consider the types.

Dr. Hauser?

DR. HAUSER: I'm not familiar with the E05 study data, but in the E03 study, at least the data that I saw suggested that there was an increased frequency of partial seizures, particularly simple partial seizures in some individuals; a decrease in generalized onset seizures, so that there are a whole series of things, but I think clearly, if one looks at big seizures, if you will, as being more severe than little seizures, an increased frequency of little seizures but a decreased frequency of big seizures, I

djj

think it would still be explained why a patient could say I can count more of these, but I'm better.

DR. WILKINSON: Thank you.

DR. COSTELLO: I would like to bring your attention to page 4-41 of my review. I broke it down by seizure types, and there was a differential response between the high and the low group. You would expect the high to do better, but in some types of seizures, they did; in other types, they did not. And in the E03 study, that was one of the other problems with the study results was that total seizures were reduced, but when you looked at partial onset seizures alone, they were not able to show a statistically significant reduction in partial onset seizures alone.

DR. WILKINSON: Well, we do now need to hear from our primary panel reviewers.

Dr. Deveraux, I guess you're first alphabetically at least.

[Pause.]

DR. DEVERAUX: Hi; I'm Michael Deveraux. I better not have any involvement with the company.

[Laughter.]

DR. DEVERAUX: I will be brief. I know that we got a late start here.

When I looked at this data--first of all, I would

djj

just like to compliment the FDA team who put this together. It was obviously a prodigious piece of work, and it was hard enough to review in the time that we had. I can only imagine how hard it was to put this together.

The one thing that, and being a neophyte to this process, never having done this before, I wasn't quite sure exactly, as I have mentioned to several of you, how to prepare this, also given the fact that there is a somewhat disparate group, ranging from world authorities on epilepsy on this panel to other individuals who don't have direct experience with epilepsy.

So, I will try to be brief, since a lot of what I had prepared to say has been so aptly covered already by other presenters. But first of all, again, just by way of a few words for those of you who are either not neurologists or who haven't had a lot of experience with this whole area, the vagus nerve is, again, to mention to you is one of 12 pairs of cranial nerves which, by its very nature, has an enormous impact on the human body. Reviewing all of the literature, I included in the handout that I made up for the--in the packet of information that I made up for the panel an article by Rutecki that appeared in a very nice supplement to Epilepsia in 1990, reviewing some of the anatomical, physiological and theoretical bases of

djj

antiepileptic effect of vagus nerve stimulation, and I, as I say, won't go over that. There were actually a few slides that were used that were also in his paper.

Again, the important point here is that the vagus nerve, particularly, stimulation of the visceral efference, which, in turn, stimulate the nucleus solitarius and then lead to widespread effects in the brain that have already been alluded to, including those areas that seem to be primary in the generation of complex partial seizures, has been shown to, in animal studies, to have an impact on clinical seizures. The theory has already been stated; in fact, the various and sundry theories that have been put forward as to why this might work have been stated, but obviously, desynchronization of brain function, of the EEG, I should say, plays an important role. And it's also one of the fascinating features that was first written about or popularized, I guess, by Gowers, but I think every epileptologist has seen this and that is that any kind of somatic stimulation in selected patients with focal seizures, some patients with focal seizures, may produce an alteration of the seizure, and so, one of the theories is that mainly, stimulation of the vagal nerve may be altering this somatic sensory pattern in the brain which, indeed, alters the seizure process.

djj

Indeed, some of these, it may be different. One can imagine that those patients who find impact from stimulation at the start of the seizure, it may actually be a different mechanism for those patients than others who find a reduction in overall seizure frequency by the pattern stimulation that has been described.

When I reviewed each one of these studies--and again, I will be very brief here, because it's already been gone over by other presenters, obviously, the two pilot studies are less important. As everybody else has stated, there has been some debate. Steve, you made some comments about, perhaps, E04 being undervalued, and one of the things I was interested in, and you as a statistician and maybe wanting to ask you a question that you could answer, and that is the wide variation between the mean seizure reduction and the median seizure reduction, in that group, the median seizure reduction in 3 months being 21.84 percent and the mean seizure reduction being only just under 7 percent.

The E03 study, one of the things that I think is important about this in the little handout I gave you is the fact that, given that this has been a fairly long study, is that the total exposure years, up to 456 years in the information made available to us, so that, obviously, unlike

djj

the E05 study, which is newer and has only a total exposure years of 135, this study has some real value from just the longevity of patient involvement.

Again, the other points to make here: the fact that 114 patients reached the 12-week evaluation of the seizure type, again, in this particular population was partial, and again, the fairly large seizure frequency of the patients in the 12-week pre-study period of six per month is a good baseline. Obviously, these were patients who were significantly impaired.

Again, just to repeat what we have already been told, that the median reduction in the high stimulation group of 24 percent and in the low, only 6 percent, which was not clinically significant, and the mean reduction is a fairly close approximate at 23.5 percent. And again, I think important to me and, as has been stressed by others from the company is that this is not going to be a device for everyone. It is going to have, like so many of our treatments for epilepsy, it is going to impact differently on different patients, and, in the high stimulation group, the fact that 30 percent of the patients had a greater than 50 percent reduction in seizure--let me rephrase that--that there was a greater than 50 percent reduction in 30 percent of the patients, again, was a very useful number.

djj

The side effects, I outlined for you again just briefly so that you can review them: the hoarseness, the cough, the throat pain, the dyspnea and the paresthesias that we have all alluded to certainly occurred with increased frequency in the high group compared to baseline and also compared to the low treatment group, the low stimulation treatment group.

The E05, again, a study which is important to point out that--and there was a 50 percent reduction in seizures. I left off the number there. It was 23 percent, which correlates fairly closely to the mean reduction in the high stimulation group, again, of 23 percent--I'm sorry, the median reduction and then the mean reduction of 28 percent.

For the reasons that have been outlined by other presenters, there was an increased amount of side effects in this group, in the high stimulation, compared to the E03 study group. The hoarseness, as we have both read and heard today, is obviously in a significant percentage of patients. It was comforting to me to hear from the patients the fact that this didn't seem to be particularly bothersome to them and again, the fact that under certain circumstances such as during presentations, the one gentleman who commented could actually and did turn off his device so that he could get through a presentation without becoming hoarse.

djj

Those were the main comments that I made. I was particularly interested, Steve, in your comments about the issue of death and mortality. Obviously, your statistical background here far exceeds my ability to look at this. As I noted, there have been 17 deaths worldwide and at least everyone involved has not thought that this was a major factor, but I'm glad you brought this up to the panel for review, and I was interested in your comments.

Now, that's mainly the presentation that I wanted to make. My feelings in reviewing all of this data are that the--and I'm not sure this is where I am supposed to say this--I felt that the company or that the device and that the studies of it that have been presented do demonstrate the efficacy and safety of the product, and obviously, one of my concerns that I mentioned earlier, and I realize in this increasingly laissez faire or this laissez faire world we live in, even with managed care, I would hope that this is a device which would be utilized primarily through epilepsy treatment centers, so that it would be correctly utilized. I don't know how we control for that; I guess we can't. But, of course, one might also argue in this managed care world that it may become increasingly difficult to use devices like this, since insurance companies and HMOs may be not as interested in paying the large up-front fee to go

djj

through an implantation.

Thank you.

DR. WILKINSON: Alphabetically, Piantadosi comes next.

DR. PIANTADOSI: May I do it from here?

DR. WILKINSON: Sure.

DR. PIANTADOSI: Well, I'm going to try to be brief also and come right to the bottom line in the interests of time. I believe also that there is a reasonably good case here that this device is effective and safe for the proposed indication. So, I will get that out first, and everything else I say, you can temper by that final conclusion.

There are some strengths and weaknesses, speaking as a methodologist here, and I have talked to this committee in the past in cases where I was uncomfortable with some of the methodologies that were used. At least here, we have nicely-done protocols; we have prospective plans for the design and execution of those protocols; we have interaction with the agency; we have a prospectively specified analysis plan. I like the inclusion of primary and secondary outcomes; the quality of life outcomes are quite important, and there does seem to be a lot of information about safety testing. So, I am quite comfortable with all of that.

djj

On the not so great side, I think there is an overemphasis and a tendency for us to think in an overemphasized way on these studies as being randomized, masked trials, and I tried to make this point earlier, although perhaps not very effectively, that the question that is randomized here, in my opinion, is not a very interesting one. It's a supportive one, essentially related to dose response. You have high versus low dose, so to speak, and you see a difference. And that is where the randomization is.

The real question of efficacy does not rely on the randomization, and I will come back to this later, I think, when we talk about labelling and how this aspect is described, but it is really a pre- or post-design. Each patient is his or her own control with respect to telling whether there has been a change over baseline, and, of course, that design doesn't rely at all on the randomization. So, I am worried in the labelling, when we describe this, and people tend to talk about randomized, masked clinical trials, we think of that as a very high standard of evidence in those cases where the randomization is between treatment A or new treatment and placebo or new treatment and standard treatment, that is, with a concurrently randomized internal control. That is not the

djj

case here, and I think it is very important to recognize that.

There are some other weaknesses. There really hasn't been very rigorous control over ancillary treatments after implantation; some attempt to control it but, in fact, we really don't know exactly whether any changes in ancillary treatments have contributed to the apparent treatment effect.

The final worry, as I said several times this morning, is over--is my concern about the death rates, and I would emphasize again that short-term outcomes or surrogate outcomes don't always fully inform us about longer-term outcomes, and I am still a little bit uncomfortable with the death rate, but I have no experience in this patient population, and if others tell me that this is reasonable and acceptable and consistent with the best clinical judgment, then, that will suffice for me.

And finally, as a methodologic point, I am not totally convinced that the percentage reduction in seizures is the right statistical endpoint for these kinds of studies, and this remark is really aimed mostly at FDA. It may be, or it may not be, but technically, my concern is that the variance estimate that we use for that outcome may not be right; it may be underestimated, in which case, the

djj

significance tests are going to show significance, perhaps, earlier than they should. That can largely be corrected by using nonparimetric estimates, but nevertheless, if the FDA is going to be in this business, I would urge them to look at that issue carefully and decide if that's really the statistical endpoint that they want for most of these studies.

The rest of my conclusions, I think, are pretty straightforward. I would like to see the mortality experience continue to be followed. I would like to see in the labelling when we come to that some characterization of the frequency of various adverse experiences, that is, quantitative description, and I would like to be very careful about how these studies are labelled in the label and not simply to toss off the term randomized mass controlled trial but rather to describe exactly the basis of the efficacy inference that is being made.

So, let me just stop there and pick up a few comments later when we get to the questions.

DR. WILKINSON: Dr. Snead?

DR. SNEAD: I will try and be brief also.

Before I get to my major concern, I have a few minor comments. First of all, to put this whole thing in an historical context, vagal nerve stimulation was really first

djj

shown to have an antiepileptic effect or antiseizure effect experimentally in 1952, and you have heard a lot of the experimental data presented today. Nobody basically has a clue as to what the mechanism for this is.

One thing that I think needs to be highlighted just for the record, if for nothing else, which I am not sure anybody has really emphasized, and that is that there is a really important difference between the animal data and the human data, and that is that in the animal data, the animal data would suggest that in order to achieve therapeutic efficacy, vagal nerve stimulation has to be done to the point of decrease in heart rate and affecting respiration. In other words, you have to see distinct physiological changes, and that is apparently not the case in humans, at least as we have heard today.

In regard to the studies that were done, I am not going to belabor the point. Suffice it to say that I focused on E03 and E05, and, from what I heard today, that may have been a mistake. But in any event, in addition to the ways in which these studies differed that you heard today, they also differed in another way, and that is that the patients in E05 were probably less refractory than the patients in E03, because patients who were surgical failures and patients who had had status epilepticus were excluded

djj

from E05. Also, I am still concerned that the statistical validity of E03 might have been clouded by the interim analysis.

I think the data wasn't presented, but in our packets, we had a series of data concerning "seizure intensity" and "seizure duration scores," and I would question the validity of those, because I didn't see where those scales were standardized anywhere.

But again, I think, in summary, the results of the E03 and E05 appear to validate the other, uncontrolled studies and show a modest but statistically significant treatment effect of about a 25 percent reduction of seizures in patients with medically refractory partial onset seizures with this device. The device appears to be safe when used and the studies presented. However, and I would like the company to respond to my however here, one of my greatest concerns is how the maximum recommended current intensity and maximum on-off ratio will be recommended once this device comes into general use. Who will do the initial programming? How will one arrive at optimal settings? Who changes the setting on a day-to-day, week-to-week, month-to-month basis once this is out there in the general population?

It was never clear to me what the maximum current

djj

intensity settings used in E03 and E05 were. The bottom line is that there are a large number of programmable variables, each with the potential to affect therapeutic outcome and/or precipitate adverse effects. Yet, there is little guidance for the treating physician that I could find in the proposed manual, who will presumably have little or no knowledge about the use of this device as to which parameters should be changed for maximum benefit ratio.

So, as I have already mentioned, it appears to me that this device is safe when used as described in the studies presented. But what about if the parameters used in E03 and E05 are exceeded? What happens?

DR. DUFFELL: It's a good question, and it's one that FDA and we have talked about previously. Actually, we felt as though there is material in the labelling covering this. Most importantly, what we recommend is that for the first initial programming of the device that the output current be started at the very lowest setting of a 0.25 milliamps and that any ramping up of the output current, whether it be at the initial visit or subsequent visits, always occur in those increments of 0.25, so, a slow stepping up. Even though, you know, most patients may end up at a value of 1.25 or 1.5, we would never want or expect that a physician should start out at that level.

djj

That would apply as well to someone who has undergone a device replacement. Again, they would repeat the process starting at the lowest treatment levels and slowly escalating up until you reach a point of comfortable patient tolerance.

The other thing about the parameters is there is language pertaining to the on-off duty cycle and not exceeding that 50 percent duty cycle which has been shown up to that point to be safe in the animal model.

DR. SNEAD: So, who is going to be doing the programming?

DR. DUFFELL: We consider this device analogous to a drug. So, therefore, prescription use of it is appropriate, and prescription dosing of the device is also appropriately prescribed by a physician. That is why patients are not allowed to--have no means of changing device parameters themselves with the magnet. The magnet can only either give a stimulation that has been preprogrammed by the physician or arrest it and stop it completely. So, only a physician--again, it's very--we view it analogous to drug dosing. It is a prescription item, and the prescription should be by a physician, not by a study nurse nor by a patient.

DR. SNEAD: And I have one final point: on page

djj

3-32 of the summary of safety and effectiveness data, the comment is made that vagal nerve stimulation is an alternative to resective surgery, and I think one has to be very careful about making those kinds of comparisons, because the data that we have seen suggests to me that the benefits of vagal nerve stimulation versus those of resective surgery are not at all similar, and the former provides a modest palliative effect, and the latter has the potential to be curative.

DR. DUFFELL: I very much agree with your remark. If you will recall my opening remarks about what we are not, we are not a replacement for resective surgery in those patients who could benefit and who are qualified for the procedure. So, I would agree with you on your observation.

DR. WILKINSON: My plan now is to have each panel member comment. So, if we could hold questions until the ball comes around to your part of the court, this is not necessarily your final chance, but it's your chance to get your final licks in.

So, Dr. Ku, would you start off?

DR. KU: I think the overall data shows that there is some effectiveness of this device, and that, used in accordance with the suggested recommendations, it probably is safe. I am a little bit concerned, still because of the

djj

significant changing in the drug dosing that was carried on during the time that the device was studied may provide some confounding influence on the validity of the data overall, but at least on a broad basis, it seems like the device is probably satisfactory.

DR. WILKINSON: Dr. Canady?

DR. CANADY: My concerns, I think, center around the issue of how we demonstrated its efficacy, particularly when we looked at the high-low or the lack of relative variability in the high-low and what I consider to be the notorious reliability of self-reporting.

In an absence of a mechanism of action; in absence of any neurophysiologic demonstration in even a small subset of the population in which we took them, stimulated them, monitored them and demonstrated some objective change in seizures, I think that I am concerned that we don't go the route of cerebellar stimulation with a procedure that becomes very popular, gives a lot of neurosurgery residents an opportunity to learn the posterior fossa and then fades.

I think that the safety issue, on the other hand, is really truly a very minor procedure from a surgical perspective, although I am not sure that in the end, the issue, at least, as a pediatric neurosurgeon, aspiration has become a much larger part of my life than I would like it to

djj

be, and I think that that is a complication that can be severely understated in terms of people's perception of why people die and why they get sick. I share their concerns about the SUDEP population. I think overall, the procedure itself is relatively trivial, is very ripe for possible abuse, but if it has some efficacy in some population, I can see it, but I don't think that the study should stop now. I think we don't know any of the fundamental issues here.

DR. WILKINSON: Dr. Spencer?

DR. SPENCER: I'd agree with many of the comments suggesting that there does appear to be data from the accumulated evidence that there is a modest effect of this device on seizure frequency, and I also think that the adverse effects, although not terribly infrequent, were not extremely severe. I am not concerned that the mortality rate is higher here, especially in light of the fact that the population of patients has a high mortality rate, and there is, indeed, accumulating evidence that patients who fail surgery may have a higher mortality rate, and when that gets figured into some of this population, that doesn't concern me as being higher than expected.

I do think there are a lot of questions that need to continue investigation, partly in terms of the kinds of seizures, and from my reading of the data, the efficacy may

djj

be somewhat greater for secondarily-generated seizures than complex or simple partial seizures, and so, I think that additional studies should continue.

My biggest concern is the level of data on efficacy in adolescents. It seems to me that that amount of data is small and has not been assessed in terms of all of the different parameters because of the smallness of the group and that it is not really possible to measure high versus low efficacy in those patients, and that is my concern.

DR. WILKINSON: Dr. Gonzales?

DR. GONZALES: I would agree that the data suggests that there is efficacy using this device in the selected population that you have used in the studies. I still have some concerns about some of the safety issues. I was surprised, but maybe I shouldn't be surprised, about the fact that patients with epilepsy using multiple drugs and a stimulator are swimming and drowning. But I think that it has to be stressed that this device should not give patients a false sense of security and that just because they have a device that seems to be working that all of the precautions that are generally given to patients should not cease and, in fact, should be stressed even more because of the sense of false security that a device like this may give.

djj

So that is, I think, a safety issue that I would like to see stressed by the manufacturers of this device and on recommendations that are given to physicians to give to the patients and directly to the patients. I think it's a very important issue.

As with Dr. Snead, I have concerns about the limitation of current of the stimulation time. I would like to know that there is a cap of stimulation; that people can't crank this up; and that there are limits to the device. And we have talked about earlier about the infection issue that I have brought up, about not knowing what's going on there, and we can assume that from the data that's been presented that a lot of the adverse effects, that as you increase the current that the adverse effects and the side effects will increase and that if there is no limit, or there is a limit such that we are going to expect more and more adverse effects, I think that that needs to be continually studied and updated.

There was one other issue that I think that finally, regarding predicting efficacy. I think that I've heard that although age, seizure type, medications and other issues don't seem to predict efficacy of the device in a group of patients that looking for indicators of efficacy are still very important, and maybe they should have been

djj

brought up earlier. But looking to predict efficacy in terms of prior to the implantation, I didn't see any data that, in fact, noninvasive--although the vagal nerve stimulator is relatively small in terms of invasiveness regarding other neurosurgical procedures, you can stimulate the vagus nerve peripherally without invasion. You can stimulate in the pharynx; you can stimulate in the esophagus; you can stimulate in other areas--the stomach--and antidromically stimulate the vagus nerve and to try to see if there are individuals where you may be able to predict some of these, so that you can screen out individuals or at least screen in individuals who happen to respond peripherally with, let's say, mucous membrane stimulation in the vagal distribution, and I didn't see any direction at all in terms of prior animal studies or human studies, and that would seem to me--there are individuals who walk around with duotube feeding tubes for months or years, and certainly, having a small wire stimulator to look at vagal stimulation long-term to see if you can predict something like this in a noninvasive way, and who knows? Maybe it will help some of these individuals? But at least, again, looking for, screening individuals for efficacy before you go to an invasive device.

There are others, but I think they have been

djj

addressed already, and so, I will leave it at that.

DR. DUFFELL: One comment, if I could address it, just one.

DR. WILKINSON: Briefly.

DR. DUFFELL: Because it has come up twice. I just want to make sure--I don't know that I was perfectly clear. The output current, I understand your concern, both of you. You have to realize that it is a rate limiting phenomenon by the patient himself. I think any of the doctors here would tell you: since this device is going on and off every 5 minutes, if they can't tolerate it, they won't leave. You know, they only go to the level of perceptibility and comfortable tolerance. You would never have an instance where a patient went home and, all of a sudden, should have a reaction to an output current, because they will have seen it before they left the office.

So, I just wanted to make sure that that was clear. But I heard all of your other concerns. Thank you for your remarks.

DR. WILKINSON: Dr. Callahan?

DR. CALLAHAN: No, I think that it's the panel's turn, if I may.

DR. WILKINSON: All right. And same with your cohort.

djj

DR. SPYKER: Yes.

DR. WILKINSON: Ms. Maher?

MS. MAHER: Well, I agree with all of the comments we have heard so far. I would just like to take this opportunity to remind the panel that I heard concerns about safety features and the safety of this device and that there are a lot of systems already in place through the regulatory requirements, such as MVR reporting and European vigilance reporting and things such as that to monitor the safety aspect so that these things can be dealt with.

DR. WILKINSON: Dr. Snead, you have given your review. Any final comments?

DR. SNEAD: No.

DR. WILKINSON: Ms. Wojner?

MS. WOJNER: It's a terrible name; Wojner.

DR. WILKINSON: I'm sorry.

MS. WOJNER: Since I'm here to represent the consumer's interests, I am going to put a little bit of a different twist on this. One of the things I would like to reiterate is my concern that this device be used by practitioners who are experienced in its use. I can't emphasize enough how strongly I agree with the comments made earlier by our colleague on this end of the table that this is a device that needs to be used in centers where

djj

excellence is known for the practice of epilepsy.

I think that the other comment that I want to make is something that I really didn't even think about making until yesterday afternoon, when I spent a significant amount of my day in the Division of Consumer Affairs, and the individuals there spent close to an hour telling me some of the wonderful experiences that they have had dealing with silicone.

[Laughter.]

MS. WOJNER: I really want to qualify my comment by saying I am quite aware of the fact that we really do not fully understand the impact of silicone on the body; that there certainly are some individuals who seem to have very different reactions and others who have no problem with it at all. Whether that is, indeed, related to silicone or the normal distribution of neuromuscular disease in the population is unclear.

But because of that conversation that I had yesterday, I wonder if we do need to add something to the packaging so that patients are aware that this is something that is contained on the device, because apparently, this has been an incredibly strong issue that the FDA has had to deal with.

DR. WILKINSON: Dr. Nuwer?

djj

DR. NUWER: I have a question, to begin with, and that is for the company on whose fingers actually are on the keyboard? I know the physician chooses the settings, but who enters the settings?

DR. DUFFELL: Actually, it could be either the physician themselves; it's certainly very user-friendly, or it could be under the direction of the physician. Again, I would see it being analogous to a drug prescription. Obviously, the patient goes home with a bottle of pills with instructions to take 300 milligrams t.i.d. It's their responsibility to take the medication as prescribed. In this case, it's the responsibility of the nurse or whoever is fulfilling the order of the physician to carry it out correctly.

Also, it is important to realize that the device also provides a printout of the program settings which are placed, generally speaking, at least, in all of our patients here in the States, in the clinic charts, so, they are subject to review and oftentimes signoff by the practicing physician just as if it were a prescription.

DR. NUWER: Because in the present labelling, there is no limit as to whose fingers are on the keyboard. It could be the nurse; it could be the EEG tech; it could be the secretary.

djj

DR. DUFFELL: There's nothing in the labelling;
that's right, correct.

DR. NUWER: Okay; thank you.

So, one of my comments would be that perhaps there
needs to be some control over or labelling about the
qualifications or oversight of the person who is actually
doing the keyboard entry of this. I also would second the
notion that's been expressed several times that at this
point, it appears that this would best serve the public to
be done in a center which has expertise in epilepsy rather
than being used generally by any medical practitioner at
this point in time.

Beyond that, I do recognize that it seems to have
very good effect in a limited proportion of these patients;
it has some positive effects in a moderate proportion of the
patients and no particular good or bad effect in another
portion of these patients. So, from that point of view, it
seems to be reasonably safe, and it does have efficacy,
although the efficacy is particularly with regard to a
limited portion of the patients, where it has very good
efficacy.

DR. WILKINSON: Dr. Piantadosi?

DR. PIANTADOSI: I just wanted to tell you that I
forgot one of my obligations, which was to comment briefly

djj

on the interim analysis, and a couple of committee members as well as an FDA reviewer had something to say of general concern about that.

Unlike many circumstances where interim analyses are done improperly or tried to be superimposed on a preexisting trial design after the fact, I don't think it's much of a concern here. If the study had been terminated early on the basis of an unplanned interim analysis, I think we could all be a little uneasy with what had taken place. In fact, that didn't happen. The plan was prospectively placed on the study. After it had gotten underway, the study actually went longer rather than being terminated earlier, and I think the general gist of the way it was handled is probably okay.

That is not to say that I endorse the way it all worked out. It's best to specify these things in the protocol and make them squeaky clean. It's hard enough to cope with issues of interim analysis on a good day, much less when you haven't followed the book. But in this case, I don't think it had any damage on what we're seeing at the end of the trial.

DR. WILKINSON: Dr. Deveraux, more comments?

DR. DEVERAUX: No.

DR. WILKINSON: Dr. Edmonson?

djj

DR. EDMONSON: Sure.

I think after really hearing all of the presentations and reviewing the data that this once again is a reminder of what medicine is, that it is really a marriage of science and art, and where the science begins and where the art begins is sort of grey. But let me just look at several areas.

First, the human impact. In the beginning, we had presentations from the patients and from the Epilepsy Foundation, and in really looking at everything, I am reminded of Hippocrates' principles; namely, we don't really focus on the disease; we focus on the person. And in that light, my impression of what has transpired is that there are patients who are benefitting from this stimulation who have--it has had a favorable impact on their quality of life.

Where the science ends to some extent is in measuring the number of seizures versus, really, probably immeasurable impact in terms of the type of seizure intensity and the variety of multifactorial issues related to being a seizure patient. So, to some extent, I think the impact in terms of quality of life would have to be placed in the GOK category, and I will clarify what that is later.

The other area that would probably go in the GOK

djj

category to some extent is the SUDEP issue, because there are a number of confounding variables here. One is that patients who are selected who are already intractable. Some patients, if we look at the surgical population, those who go on to resective therapy for seizures with a SUDEP incidence of 9-plus percent and folks in the E05 study with, even if you include the drowning, of seven point something percent.

Again, the GOK issue there is that we really don't know what causes SUDEP. That's one; two, that in looking at these data, there are some things that we can't clairvoyantly assess, and I think these are issues that may have to be addressed at a postmarketing level, because the SUDEP issue, for example, may require 10,000 patients to tease out some of these factors.

So, I think, from a practical standpoint, that enough evidence has been presented to support efficacy, and, in balance, looking at everything, the risk in adverse effects seems to be within an acceptable range, and there are many other factors that, as I mention, are in the God only knows category and will have to be left at that, and that is where we rely on art.

DR. WILKINSON: And my comments, my understanding of the difference in the animal studies, the need in the

djj

animal studies to create cardiovascular effects is that the animal study included the cardiac branch; in the human, the left vagus was chosen to avoid the cardiac branch, and so, I have no problem with that if we are dealing primarily with afference.

That does have an impact, however, on the labelling, and if the left vagus is to be used, then, left vagotomies should be an exclusion criteria.

I would also harken back to one of our patients, who was on five drugs and had a good response to this device, and I would eliminate from the labelling up to three drugs. I think that is a clinician's call. If the patient is taking five drugs, that should not exclude the patient.

Under the exclusion criteria for the study, cardiopulmonary disease or peptic ulcer were allowed to exclude patients. I would like to know what is the current recommendation if this device is approved. Have you proven whether it is dangerous for this population? Or is that a guess?

DR. DUFFELL: That was based on a theoretical concern, based upon what we know physiologically about vagus intervention. Currently, what the labelling says--and I can't recall the section, but I am sure--okay, I'm being helped out here; it's on page 212 of the labelling--what we

djj

do here is we actually, and I think this is one of the issues that the panel was to consider anyway--was this list of things that we don't have necessarily experience in. I think for me to be able to claim that I can treat patients with that condition, I certainly would have needed to have studied them, and obviously, as you know, I did not.

So, right now, the labelling, for that reason, just says that the safety and the efficacy of this therapy has not been systematically established in these patients with the following conditions. So, you know, that's the only response I think I can give to you.

DR. WILKINSON: Systematically may be a little bit of a caveat there.

DR. DUFFELL: Yes.

DR. WILKINSON: Well, my overall impression of this device calls to mind the Model T Ford. I think 50 years from now, 25 years from now, when we look back today to a step forward in a new arena, this device may be a Model T Ford. But the Model T Ford changed transportation in the United States, and so, my impression is that we do have data that shows the device can be effective. We have very little concern about the direct damaging effects of the device, even though its improper application certainly could be damaging. That's really not the problem of the device but

djj

of the user. And so, my own personal impression is that this is a useful addition to the armamentarium of the epileptologist.

Now, we need to take specific votes on each of the questions proposed to the panel. I have asked the primary clinical reviewers if they would comment about each question: should the question be allowed to stand, or would they suggest modifiers to the question before we have a show of hands vote.

All right; the first question you see here: adequate demonstration of safety and effectiveness. Do either of our primary reviewers wish to recommend a modifier to that?

DR. SPYKER: If I could interrupt, the intention of this is to ask is there enough to proceed. It's to try to avoid the conundrum we seem to have gotten ourselves into last time, where we had to say, well, assume it's effective and develop some labelling. So, this is really to say is there enough data to proceed with the evaluation. And I am not convinced you have to vote on every one of these. I think the ultimate decision is on the last question: is it effective as labelled. But I certainly would be happy to have you proceed any way you like. But we don't require a vote on anything but the final question.

djj

DR. WILKINSON: Any other panel comment about this?

So, we are, in a sense, putting the most important question at the beginning here, but I would like a show of hands from the panel. All of those who believe that the data has adequately demonstrated the safety and effectiveness of the device, the voting members of the panel.

[Show of hands.]

DR. WILKINSON: All who feel that the data has not demonstrated effectiveness.

[No response.]

DR. WILKINSON: So, we seem not to have any objections.

Now, indications: this is question number two. Does this adequately describe the patient population? I have already objected to the up to three antiepileptic medications.

DR. DEVERAUX: I certainly agree with your statement, too, and, in fact, it doesn't really say: is that serially? Is that consecutively? You can imagine, in certain circumstances, an individual not responding to any drug very effectively only being on one or two medicines. So, I don't think that you have to have polypharmacy to make

djj

the decision, whether it is consecutively or serially, and I would like to leave that up to, as you, yourself, so nicely stated, up to the physicians.

DR. CANADY: You might want to state, however, that it should be used as an adjunct to therapy, since we have no situations in which it is used independently.

DR. DEVERAUX: Yes; that's in the first paragraph.

DR. CANADY: We do need to say that part.

DR. DEVERAUX: Sure.

DR. WILKINSON: As an adjunctive therapy. So, that would be left in.

Yes?

DR. PIANTADOSI: I would just like to see the second sentence removed. I think the first sentence is clear enough.

DR. DEVERAUX: The first sentence is clear.

DR. WILKINSON: All right; then, let's accept that as a modification that the recommendation to eliminate the second sentence. Would the panel then agree to the adequacy of the definition in the first paragraph under 2., indications?

All who think this is an adequate definition, would you just raise your hand?

[Show of hands.]

djj

DR. WILKINSON: And seeing no objection; all right.

DR. SNEAD: Can I make a comment?

DR. WILKINSON: Yes.

DR. SNEAD: I think if you leave the first sentence in, my view is that the data that we have seen are for medically refractory partial onset seizures. And I think that term should be used.

DR. WILKINSON: Does the panel generally agree with that? Any objection to that?

[No response.]

DR. WILKINSON: No.

DR. PIANTADOSI: Could I point out one other thing, too, just to be absolutely clear? The same sentence occurs in the patient labelling on page 3, and I presume the same opinion would apply.

DR. SPYKER: You may presume we will make the patient labelling consistent with this final labelling.

DR. WILKINSON: Question three.

DR. EDMONSON: Yes, just one question--

DR. WILKINSON: Yes.

DR. EDMONSON: --to Dr. Spencer and Dr. Canady, because on that side, there was some query about adolescents and the efficacy data, so I just wanted to revisit that.

djj

DR. SPYKER: Could you speak into the microphone, please?

DR. EDMONSON: I just wanted to revisit the efficacy data for adolescents and to punt to the other side of the table, Dr. Spencer.

DR. WILKINSON: That's really question number three.

DR. EDMONSON: Oh, okay.

DR. WILKINSON: Yes; let's have the question number three, if we may: do the data support this age cutoff, or should another age be used? Should there be zero age, no age recommendations? Should there be a different age recommendation?

Do the primary reviewers have comments?

DR. DEVERAUX: I'm not--having gone over the data, I was a little unclear, at least from the methodological standpoint, why you would necessarily exclude younger children, and, in fact, E04 included children, I think, down to the age of 2. I'm not quite sure what to do with this. I certainly wouldn't want to exclude, again, in highly sophisticated centers with pediatric epileptologists, I wouldn't want to take this tool out of their hands, absolutely. And I don't know quite how this should be done to do that.

djj

There may be certainly circumstances where this would be very effective in an 11-year-old. So, I think just to use chronological age here kind of bothers me a bit, but again, I would pass to the pediatric neurosurgeon and neurologist in the group.

DR. SPYKER: Well, we didn't put the age in the contraindications. I mean, that would be the only place where I would consider where it would be illegal, if you will, to use it. So, this is sort of the next level of severity of restriction.

DR. CANADY: Another alternative might just be to mention that the numbers for children less than 12 are limited at this time, and that gives you the--

DR. SPYKER: Right; one thing you might consider doing or please do consider doing it in each of these is if you have some specific suggestions, in other words, either in terms of a design or in terms of the number of patients you would like to see studies, we certainly want to provide--part of the reason that we would leave something like this in a label, too, is to provide some incentive to get some good science done in this age group. So, if you have some guidelines that you could suggest to us or that you are willing to work with us on devising those, we would be happy to have your help.

djj

DR. WILKINSON: Dr. Spencer, what's your feeling?

DR. SPENCER: I just think that there needs to be an investigation of its efficacy and safety in younger children, and the current data don't support this or any other age cutoff. I mean, there hasn't been, to my judgment, good investigation in children, though it is certainly true that there may be adolescents and younger children who would have the same kind of response as the older patients.

So, I would like to see some wording that would support the specific investigation of that younger population.

DR. WILKINSON: Would you be more comfortable with shifting the age to the paragraph of lack of information: there is, at this time, insufficient information regarding its effectiveness and safety under age 12?

Any other comments about that suggestion? Dr. Sneed?

DR. SNEAD: I think that's a reasonable suggestion. I would like to just say a word of caution about including children at this date. First of all, I am not convinced that we have data to do that. Secondly, what we have heard about today are that the patients will tell you when the stimulus is too high, because they are

djj

uncomfortable, because of the voice change. Well, some children are not able to do that, and some children are severely neurologically handicapped; some children are too young, and you really need to be very careful about extrapolating these data into that kind of population.

DR. WILKINSON: Any other comment, then, about this question?

DR. SPYKER: I'm not sure I understood the suggestion. We already have it back in the has not been shown effective. That's on page 12, and I guess, well, so, the question stands: do we want to leave this in the indication section. I don't propose that we remove it from back in individualization of treatment?

DR. WILKINSON: It's already in that paragraph.

DR. SPYKER: Yes, sir. Thank you.

DR. WILKINSON: Yes. So, leaving it in this paragraph would emphasize the lack of data for the 12-year-old age cutoff, but not listing it as an absolute contraindication would still leave the clinician some leeway, so, perhaps leaving this in does make sense.

DR. DUFFELL: Could I make a comment on that?

DR. WILKINSON: One quick comment.

DR. DUFFELL: I agree with what you're saying, but what we also need to remember is that what the indications

djj

state also greatly influences what the payers will pay for. So, the panel needs to consider that as well. We will work with the FDA to constructively work out whatever the label should be, but I wouldn't want you to neglect that in your considerations as well.

DR. WILKINSON: And also, the future will come, and with the future may come data.

[Laughter.]

DR. WILKINSON: And if we have data, then, the labelling can change.

My suggestion would be that we vote to support this. And so, I propose that we have a show of hands on the question as labelled; that the data collected so far support leaving the language as it is.

All in favor of leaving the language as it is.

[Show of hands.]

DR. WILKINSON: All who oppose that.

[No response.]

DR. WILKINSON: All right.

Now, question 4 has already been answered.

Question 5 is the question that I raised about unilateral vagotomy. And unless there are other comments, I would propose that the question be changed cannot be used in patients after a bilateral or left cervical vagotomy.

djj

Discussion?

DR. DEVERAUX: What about individuals who have a right cervical vagotomy? I'm again throwing this question out. Would there be issues, then, with stimulating the one remaining, good, vagus nerve? That's a question that I have no knowledge base. I'm just wondering if this should be an individual who has either or, left or right, or bilateral.

DR. WILKINSON: We certainly have no data to support that prohibition, but the data is all based on the use of a left vagus nerve.

DR. CANADY: I would think in America now, the most common cause of loss of a right vagal nerve is anterior cervical fusion. I mean, general surgeons don't cut cervical vagi. They don't get a chance to do much cutting of the vagi at all now. So, I'm not sure we even know. Most patients who have vagotomy for ulcer disease have intact cervical vagus.

DR. WILKINSON: So, I would propose the question, then, to be voted on: cannot be used in patients after a bilateral or left cervical vagotomy. All who believe that is a reasonable statement--

[Show of hands.]

DR. WILKINSON: Any opposed to that?

[No response.]

djj

DR. WILKINSON: All right.

Question six, individualization of treatment is that paragraph of therapy not established adequate. We have already commented on two aspects of that paragraph. Do primary reviewers or any other panel members have comments?

DR. CANADY: You know, having come as a neurosurgeon off the pedical screw experience, I wonder if we may not want to, from the physician perspective, want to make a statement because of the category of disease with which we are dealing, in which we have medically refractory disease, because the absence of it in the contraindications may not be sufficient protection.

DR. WILKINSON: What would you specifically add?

DR. CANADY: Say that in view of--in this population of medically refractory epileptic patients, individualization of treatment may, outside the specific indications, could have a role. In other words, anybody who puts it in in a child less than 12 is going to be at some tort risk unless we--

DR. WILKINSON: That, perhaps, we could have some guidance from somebody from the FDA. Putting some sort of language like that, is that customary? Is that helpful? Is that useful?

DR. CALLAHAN: I think only when it is put in as a

djj

contraindication do you get into the torts and the legalities of it. This is just saying, instead of saying has not been systemically established, it really hasn't been studied, and there are other ways of saying it.

DR. CANADY: My understanding of the pedical screw was that it was not contraindicated in the uses for which the people received it.

DR. CALLAHAN: The problem with the pedical screw is that that was not even approved for any indication.

[Laughter.]

DR. CANADY: I'm willing to defer.

DR. WILKINSON: All right; so, any other discussion of this item? Basically, the panel is in agreement with the list as stated on page 2-12.

All who are willing to accept that list, raise your hand.

[Show of hands.]

DR. WILKINSON: Any who feel there should be modifications or would not accept the list.

[No response.]

DR. WILKINSON: All right.

Question number seven is an open invitation for comments from the floor, for questions from the floor.

Dr. Snead, did you have a suggestion?

djj

DR. SNEAD: Yes; one of the things that I didn't see in the potential labelling was the issue of the body scan. We were told that the body scan in a patient with this device is dangerous. And does that mean that if you have one of these devices implanted, whether it is on or off, a body scan is precluded in you? Because if that is so, that should be spelled out in the labelling.

DR. WILKINSON: I think it is in the labelling.

DR. KU: As a radiologist, it would be a contraindication to scanning, period, due to the heating problem.

DR. SNEAD: But the patient needs to know that.

DR. SPYKER: I will be willing to commit that that will occur in the patient labelling.

DR. KU: Okay.

DR. WILKINSON: And that, I believe, is in the labelling.

DR. SPYKER: It's in the physician labelling, yes.

DR. WILKINSON: Yes.

Dr. Piantadosi, any other suggestions for labelling?

DR. PIANTADOSI: I have two residual concerns. One is on page 2-9, dealing with potential adverse events, a couple of which are the same as those in table one, which

djj

are not potential but are real, and I just wonder if those lists couldn't be reconciled with one another, and it might also be helpful to try to give some quantitative assessment of the list under 6-2 to the extent that it is different from table one, some sense of the frequency with which those occur, even if it is just a crude up or down.

My second concern is on the next page, 2-10, and deals with table two in the description or the types of studies. As I said in my comments, I am a little concerned that somebody reading across the first line there will see randomized parallel double-blind and will completely misinterpret the nature of those studies. I think I could probably argue that table two doesn't even need to be in the labelling, but if it is, I would like to see more careful description of what E03 and E05, the nature of those studies rather than just simply tossing off the term randomized, double-blind trial.

DR. WILKINSON: So, do you have a wording suggestion?

DR. PIANTADOSI: No, I actually didn't think of specific wording, but I think as long as the agency is aware of the issue, if they wanted to offer something a little more specific about how the studies are described, I would be satisfied with whatever you come up with.

djj

DR. SPYKER: This would be a wonderful opportunity for us to work together on this. We would be glad to make a proposal, and you can take a look at it.

DR. PIANTADOSI: I'd be happy to do that.

DR. SPYKER: That would be great. We'll do that.

DR. DEVERAUX: Would this be the appropriate place--and again, I don't want to put language into labelling that just confounds everything--but several of us have been concerned about who is going to use this device, and would it be appropriate to put something to the effect in that it is recommended that neurologists and neurosurgeons with special expertise in epileptology be involved in the utilization of this device or something to that effect?

DR. WILKINSON: From the FDA perspective, is that precedent-setting or customary?

DR. SPYKER: Well, we have been, traditionally and more recently, early in the precautions section of who should be using this. As you see, you put a little separate section. This is the second section, on who the prescribing physician. There is also a paragraph there on implanting physician. Again, if somebody--this is our first cut on this, and if somebody wants to work with us and beef this up some, we would be glad to do so. We wanted to draw the

djj

distinction, and we wanted to get a little bit of guidance and a reminder to them to look to the individualization of treatment section, which, right now, I admit, is a little anemic, but we hope to punch that individualization of treatment section up a little bit more.

DR. WILKINSON: So, you're willing to strengthen that a bit and include some more general experience in the treatment of epilepsy.

DR. SPYKER: I guess our thinking was the most important--I don't know who did this word processing, but yes, I think this ought to be strengthened some. Perhaps you can offer some suggestions, too. We thought training was the most important thing. We didn't want to say it needs to be a pediatrician or it needs to be an epileptologist.

DR. EDMONSON: Except the training in the initiation of the device seems relatively trivial in a sense, and the question is in whom to implant it rather than how it functions once it's implanted.

DR. WILKINSON: We've already heard that they have been implanted by vascular surgeons and others who don't even know the brain exists.

[Laughter.]

DR. CANADY: And associated with a proper

djj

epileptologist, probably, honest-to-gosh, good general surgeon could implant it as well as anybody else. I mean, the territory falls well within a number of surgical territories. So, I am not so much concerned about the process of implantation either; it's really the process of decision making.

DR. WILKINSON: But the prescribing is really the key.

DR. CANADY: Yes, the prescribing of the device, not the settings.

DR. WILKINSON: Right, not the mechanics of putting it in.

DR. CANADY: Right.

DR. SPYKER: For the implanting physicians, we have put some bullets and said they really need to do these few things, not because this is simply a wonderful package but to remind folks that there are a number of things.

DR. WILKINSON: And I don't think anyone has problems with that. It's who makes the decision to recommend it to a given patient, and that's what Dr. Canady is saying and what we have heard Dr. Deveraux say, that that decision should be made by a person who is familiar with the broad range of treatments available and experience in epilepsy.

djj

DR. SPYKER: One thing we easily can do is put prescribing physician first, because they are the ones making the decisions.

DR. WILKINSON: Right.

DR. SPYKER: So, that's a simple thing to do.

DR. KU: I have a suggestion: since it looks like we're going to approve this device, is it possible to consult one of the epilepsy societies to provide some guidelines as to, you know, when this device would be properly utilized?

DR. SPYKER: Well, let me suggest two things: one is that one or more of the panel help us craft this wording and that we do that post-approval that that be the decision. I don't want to hold up approval to get a society involved in doing this, but I would like very much to have some help with crafting the wording. So, I'd like to do both of those things.

DR. WILKINSON: We certainly have a paragraph about indications and so forth.

Now, the next five questions really relate more to questions of future study, and I don't think we need to look at those specifically--the next four, 8 through 11, about future studies, I think, are the principal questions raised here: should further studies be done?

djj

Does the panel have recommendations regarding further studies other than what we've already discussed?

Dr. Ku?

DR. KU: I think--would it be possible to do post-market surveillance on the efficacy to get additional data? That may help the company, also, with their evaluation of the under-12 population if the company is interested in pursuing that end. But I think overall, there is data on 400-some patients. They may have more powerful statistics if that number were increased.

DR. WILKINSON: And I believe that is a requirement now, is it not, the post-marketing surveillance?

DR. DUFFELL: I couldn't hear all of that. Could you repeat it?

DR. KU: I guess, well if it is a requirement for post-marketing surveillance, then, that is already built in. I'm thinking that with the post-marketing surveillance, that would provide additional data to either buttress or defeat the efficacy of this particular product. It would also, probably, help address the issue of the under-12 population, especially if your company is interested in pursuing that particular end.

DR. WILKINSON: Then, I think the final question that we need to decide is the bottom line question.

djj

Yes, Dr. Piantadosi?

DR. PIANTADOSI: I'm sorry to interrupt. I just wanted to be sure about those four questions. We're not talking about conditional approval, are we?

DR. WILKINSON: No.

DR. PIANTADOSI: Okay.

DR. WILKINSON: And that's not my impression, no, and that's where this last question comes in.

I would like to offer for a vote the question should the panel approve this device as having adequately demonstrated its safety and effectiveness? And should this panel recommend its approval to the FDA?

Any discussion from the panel?

May we have a show of panel recommending approval of the device?

[Show of hands.]

DR. WILKINSON: And with that, I think we have last statements from Mr. Keely.

MR. KEELY: No, I just have a question about the vote. I think I am unclear about the vote again. I seem to be kind of thick at the vote time. It sounds like you approved it with no conditions and as it is, and I don't think that's what you meant to do.

DR. WILKINSON: Well--

djj

MR. KEELY: Because it sounds like you had a lot of labelling recommendations and post-marketing surveillance and a few other things which really are conditions of approval, I believe.

DR. WILKINSON: Well, we are assuming that those conditions are going to be met, I think, because--

DR. CANADY: Well, why don't we just do it again?

[Laughter.]

MR. KEELY: First of all, to follow the routine of the way we should be voting, we should have a motion presented, and I believe that that was discussed that it should be presented or could be presented by one of the primary reviewers and then have it seconded and discussion and amendments made or changes made to that motion and a vote taken at that point.

DR. WILKINSON: Dr. Snead has risen to the occasion.

DR. SNEAD: Yes; I would like to move that we approve this device with all of the labelling caveats that we've been talking about for the last hour.

DR. WILKINSON: Any second to that?

DR. EDMONSON: I second that.

DR. KU: I would like to make an amendment to that.

djj

DR. WILKINSON: Amendment?

DR. KU: To include post-market surveillance.

DR. WILKINSON: Is the amendment acceptable?

DR. SNEAD: Yes.

DR. WILKINSON: Any discussion from the panel?

MR. KEELY: Can we have a listing, so we are clear, of what the conditions are, please?

DR. WILKINSON: They're the first seven questions.

DR. SPYKER: I feel like we've captured the spirit. I am comfortable that we could carry out the panel's recommendations with regard to the labelling, which is typical at that point. You know, that's our job. We can handle this.

DR. WILKINSON: Good man.

Hearing no further discussion and overriding our fearless leader, perhaps--

[Laughter.]

DR. WILKINSON: --can we have a show of hands, then, on the motion as proposed, second, modified and otherwise massaged?

[Laughter.]

DR. WILKINSON: All in favor, please raise your hands.

[Show of hands.]

djj

DR. WILKINSON: Has the vote been recorded?

And then, all opposed, please raise your hand very high.

[No response.]

DR. WILKINSON: All in favor of adjournment--or do you have last comments?

DR. DUFFELL: And we'd like to make a last, closing comment as well.

DR. WILKINSON: If it's 30 seconds or less.

DR. DUFFELL: It's real quick. We just want to thank you all for your time and consideration. I happen to sit on an advisory panel myself, so I know the time and commitment that is involved in getting prepared for it. Obviously, you were prepared, and we appreciate your questions.

Thank you very much.

DR. SPYKER: And the agency would certainly like to thank the panel members for this outstanding job.

MR. KEELY: Yes.

Please leave the materials at your desk if you don't want to take them with you. And if you take them with you, they need to be otherwise taken care of, burned or shredded. So, it is probably best to leave it here.

Thank you for your participation. We will see you

djj

the next time.

[Whereupon, at 3:58 p.m., the meeting was
adjourned.]

- - -